Direct Current Auditory Evoked Potentials During Wakefulness, Anesthesia, and Emergence from Anesthesia

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Direct current auditory evoked potentials (DC-AEPs) are a sensitive indicator of depth of anesthesia in animals. However, they have never been investigated in humans. To assess the potential usefulness of DC-AEPs as an indicator of anesthesia in humans, we performed an explorative study in which DC-AEPs were recorded during propofol and methohexital anesthesia in humans. DC-AEPs were recorded via 22 scalp electrodes in 19 volunteers randomly assigned to receive either propofol or methohexital. DC-AEPs were evoked by binaurally presented 2-s, 60-dB, 800-Hz tones; measurements were taken during awake baseline, anesthesia, and emergence. Statistical analysis included analysis of variance and discriminant analysis of data acquired during these three conditions. About 500 ms after stimulus presentation, DC-AEPs could be observed. These potentials were present only during baseline and emergence—not during anesthesia. Statistically significant differences were found between baseline and anesthesia and between anesthesia and emergence. In conclusion, similar effects, as reported in animal studies of anesthetics on the DC-AEPs, could be observed in anesthetized humans. These results demonstrate that DC-AEPs are potentially useful in the assessment of cortical function during anesthesia and might qualify the method for monitoring anesthesia in humans.

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Monitoring depth of anesthesia remains a problem in the management of anesthesia. Several approaches have been taken, mostly based on measuring cortical electrical activity, to develop monitoring devices that combine high sensitivity, reliability, and easy handling in an operation room setting. Auditory evoked potentials (AEPs) have been investigated as possible monitoring variables, and most of the short-, middle-, and long-latency components of AEPs have already been examined for their sensitivity to anesthesia (1). In addition to these transient, or AC, components, event-related potentials also contain sustained, or direct current (DC), components. DC potential responses to sustained acoustic stimuli are an excellent indicator of the integrity of cortical sensory processing in the cat. The cortical DC response of the primary acoustic cortex showed a dose-dependent reduction to anesthetics, and it disappeared during deep anesthesia (2,3). Thus, DC-AEPs could be used for monitoring depth of anesthesia. However, their sensitivity to anesthesia in humans has not been investigated. In an explorative study, we aimed to investigate whether similar effects on DC-AEPs could be observed in anesthetized humans. We administered anesthesia for 20 min in 19 healthy volunteers and simultaneously recorded DC-AEPs via 22 scalp channels. Because of the growing importance of total IV anesthesia and to exclude effects specific for a single anesthetic substance, we used two different short-lasting IV anesthetics. We hypothesized that DC-AEPs would show significant differences between the awake, anesthetized, and emergent states.

Methods

After approval from our medical ethics committee and the obtaining of signed written informed consent, 19 male right-handed volunteers were included in the study (median age, 23 yr; range, 20–28 yr). Handedness was determined by using the Marian Annett Handedness Inventory (4). All subjects were classified as ASA physical status I, showing no sign or history of

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acute or chronic disease, organ impairment, or use or abuse of drugs known to affect cerebral activity. Single-blinded randomization to the Propofol or Methohexital Group was accomplished by means of a computer generated randomization list (Microsoft Excel™ 7.0; Microsoft, Redmond, WA). Experiments took place in a separate room of an intensive care unit and were isolated to the surroundings, thus assuring undisturbed conduct of the protocol.

In the first condition, 60-dB 800-Hz tones of 2-s duration were presented binaurally to the awake and fully aware subject via standard stereo earphones. To allow comparison with anesthesia, subjects had to close their eyes during this baseline condition. The interstimulus interval of the tones varied from 5 to 14 s, the mean interval being 9.5 s. In total, 75 tones were presented to each subject (duration approximately 15 min). After this condition, anesthesia was induced by using propofol in 10 and methohexital in 9 subjects. Auditory stimuli were presented in the same manner as during the first condition (except that the total number of presented tones was higher because of the longer duration of this part of the experiment). Tone presentation and electroencephalogram (EEG) recordings began shortly before the induction of anesthesia and continued until the reoccurrence of the eyelash reflex.

Several aspects have to be considered to obtain sufficiently stable topographic scalp DC-AEP recordings (5,6). One requirement is to avoid or reduce distortions of the electrode-skin interface by mechanical influence (e.g., head movements). This makes the use of an electrode cap impossible, because caps do not provide independent recording sites. Thus, 22 nonpolarizable Ag/AgCl electrodes evenly distributed over the scalp were mounted onto small plastic adapters. These adapters were glued to the scalp with collodion (6). Electrode positions on the median sagittal line (Fz, Cz, Pz, and Oz) corresponded to those of the international 10-20 system, whereas the others only approximated them. They will be referred to as Fp1′, Fp2′/F7′, F3′, F4′, F8′/T3′, T4′, T5′, T6′/C3′, C4′/P3′, P4′/O7′, O3′, O4′, and O8′. To avoid skin potentials, known to show a similar time course as DC-AEPs, the skin at each location was scratched with a sterile single-use needle until a minute amount of blood was drawn. This additionally kept electrode impedance <1 kΩ (controlled by measuring the input impedance of each electrode). Adapters were filled with a commercially available but degassed electrode gel, and electrodes that were prefilled with the gel at least 30 min before application were clipped onto the adapters. Degassing is mandatory because macroscopically invisible bubbles contained in the gel might migrate to the electrode surface because of thermal effects and alter the electrode potential, resulting in slow drift artifacts. All electrodes were connected to a high-input impedance ($\geq$100 GΩ) multichannel DC amplifier (resolution, 0.5 microvolts per bit with a 16-bit A/D converter) developed in the Brain Research Laboratory, Department of Psychology, University of Vienna (5), with an excellent technical baseline stability (<10 μV/d). All EEG electrodes were referenced to linked mastoids, and a ground electrode was placed on the forehead. Because eye movements and eye blinks produce artifacts of considerable amplitude, horizontal and vertical electrooculograms were recorded bipolarly from 2×2 electrodes (mounted above and below the right eye and outer canthi, respectively). Data were recorded in the frequency range of DC to 100 Hz (notch at 50 Hz), sampled at a rate of 4 kHz, and then downsampled for digital storage. Downsampling rate in this study was 62.5 Hz. Because subjects were supine during anesthesia, mechanical pressure on the occipital electrodes was avoided by placing a roll made out of foam plastic beneath the subject's neck and by additional manual stabilization of the head. With the use of this additional provision and the standard laboratory recording setup, highly stable and reproducible DC recordings could be obtained.

Volunteers were monitored with a five-lead electrocardiogram, a blood pressure cuff, and a pulse oximeter. An 18-gauge IV cannula was placed in each arm, one for the administration of drugs and fluids, the other for obtaining blood samples. After the baseline measurements, the volunteers were placed in the supine position, and injection of the anesthetic drug commenced. In the Propofol Group, subjects received an IV bolus of 3–4 mg/kg of propofol in increments (Diprivan™; AstraZeneca, Basiglio, Italy) until loss of consciousness (loss of eyelash reflex), followed by a continuous infusion of 3 $mg \cdot kg^{-1} \cdot h^{-1}$. In the other group, methohexital (Brietal™; Lilly, Indianapolis, IN) 1–2 mg/kg IV was injected until loss of consciousness, followed by a supplemental bolus of 0.5–1 $mg \cdot kg^{-1} \cdot h^{-1}$. When spontaneous breathing stopped, the volunteers were ventilated by mask (Sulla™ 900; Dräger, Lübeck, Germany). A stable anesthetic state, as evaluated by clinical signs (e.g., blood pressure, heart rate, and vegetative signs), was maintained for approximately 20 min until all measurements were obtained. Then the administration of anesthetics was stopped, and the volunteers were allowed to emerge.

Venous blood samples were drawn after the anesthesia induction, during stable anesthesia, and after return of the eyelash reflex. Samples were centrifuged and stored for further processing at -20°C. Because of technical reasons (defect of the refrigerator), samples from only 10 volunteers (7 with propofol and 3 with methohexital) could be used for measurements. Therefore, no statistical evaluation was performed, and these data will be presented only descriptively. Propofol and methohexital concentrations were measured

with gas chromatography and mass spectrometry. Calibration curves were linear over a range measured from 0.01 to 10 μg/mL, and a limit of detection of 0.01 μg propofol and 0.01 μg methohexital per milliliter of plasma could be achieved.

Because only trials judged to be free of artifacts should be used for averaging, data were visually inspected off-line, excluding trials assessed to contain artifacts from the analysis. Artifacts caused by eye movements and blinks were removed with a linear regression approach (7).

After removal of artifact-containing trials, stimulus-linked averages of trials of baseline, anesthesia, and emergence from anesthesia were calculated for each subject. Because background EEG amplitude increased during anesthesia compared with baseline, trials of all three conditions were digitally low-pass filtered (frequency range, DC to 5 Hz) before averaging. The number of trials included in each average was kept constant to make signal-to-noise ratios comparable among averages. For the baseline condition, the average was computed by randomly selecting 40 of the 75 available trials. Forty consecutive trials during steady-state anesthesia were selected for the anesthesia average, whereas the 40 trials before the reoccurrence of the eyelash reflex were used for the emergence average. In addition, to make sure that only trials representative of the respective conditions were used for averaging, every trial was visually characterized for frequency, amplitude, and topography and classified as belonging to one of four phases (baseline, initial changes after bolus, steady-state anesthesia, and return to baseline patterns). In addition to the subject who had to be excluded because of a laryngeal spasm, 2 of the remaining 18 subjects had to be excluded from the analysis because of technical problems. The final sample consisted of nine subjects in whom propofol and seven in whom methohexital had been used as the anesthetic.

For statistical analysis of the DC component of the AEP, the mean DC amplitude of the interval 500 ms after stimulus onset until stimulus offset was computed relative to a 1000-ms prestimulus mean DC amplitude baseline. By starting at 500 ms, we ensured that the early and transient AEP components were excluded from computation, yielding a true DC value during the specified interval (Fig. 1). With this value, we performed univariate analyses of variance (ANOVAs) to assess the effects of the experimental conditions on the DC-AEP. For easier interpretation, three analyses—comparing two conditions each—were computed instead of one large ANOVA that included all three conditions. Factors were GROUP (k = 2 levels; propofol vs methohexital), STATE (l = 2; either baseline, anesthesia, or emergence), and LOCATION (m = 22; 22 electrodes). Because ANOVAs always included the repeated measures factor LOCATION, the problem of nonsphericity had to be considered (8). Consequently, degrees of freedom were adjusted according to the procedure suggested by Greenhouse and Geisser (9) when violations of compound symmetry were observed. The significance level was $\alpha = 0.05$. Degrees of freedom, ϵ[Greenhouse and Geisser (9)], ϵ-adjusted P value, and effect size (η^2) are reported. The η^2 was used to assess the amount of variation explained by the independent variables used in the analysis. In addition to testing omnibus effects via ANOVAs, *a priori* linear contrasts of specific electrode configurations were computed to evaluate whether differences between states could be shown with the information provided by these electrodes alone. All contrasts were based on specific error terms caused by violations of the sphericity assumption (10). The fronto-medial electrodes (F3′, F4′, and Fz) were considered as most reliable in the detection of DC-AEP differences because it had been repeatedly documented (11–13) that DC-AEPs are most prominently reflected in this area. In addition, we tested whether the observed effects were also specific for the modality in which stimuli were presented by contrasting occipital electrodes (O7′, O3′, Oz, O4′, and O8′) picking up activity from the visual cortex, which were not expected to show any significant differences. As a complementary approach, we performed discriminant analysis to evaluate the diagnostic utility of the DC-AEPs more directly.

Hemodynamic and oxygenation data of the groups were compared by a Student's *t*-test for unpaired samples. All analyses were computed with SPSS™ for Windows 7.0 (SPSS Inc., Chicago, IL) and cross-validated with STATISTICA™ 5.1 (1997 edition) (StatSoft, Tulsa, OK).

Results

Duration of anesthesia was 24 ± 4 min in the Propofol and 26 ± 4 min in the Methohexital Group. Hemodynamic data showed significant differences between the groups, whereas oxygenation was not different (Table 1). Anesthetic blood concentrations were as follows: propofol (median [min; max]) was 10.8 (9; 30) μg/mL after induction and decreased to 5.5 (1.5; 16.8) μg/mL during anesthesia. At emergence, 1.3 (1.1; 4.6) μg/mL was measured. Methohexital decreased from 14.8 (12.2; 18.3) μg/mL to 5.1 (3.4; 8.1) μg/mL and further to 2.8 (2.4; 6.5) μg/mL.

The DC-AEPs in Figures 1 and 2 present the main results. In the baseline condition, starting at approximately 500 ms poststimulus onset, a sustained response clearly distinguishable from the transient potentials after onset and offset of stimulus presentation was evoked over frontal, central, and parietal areas with maximal amplitude at fronto-medial electrode

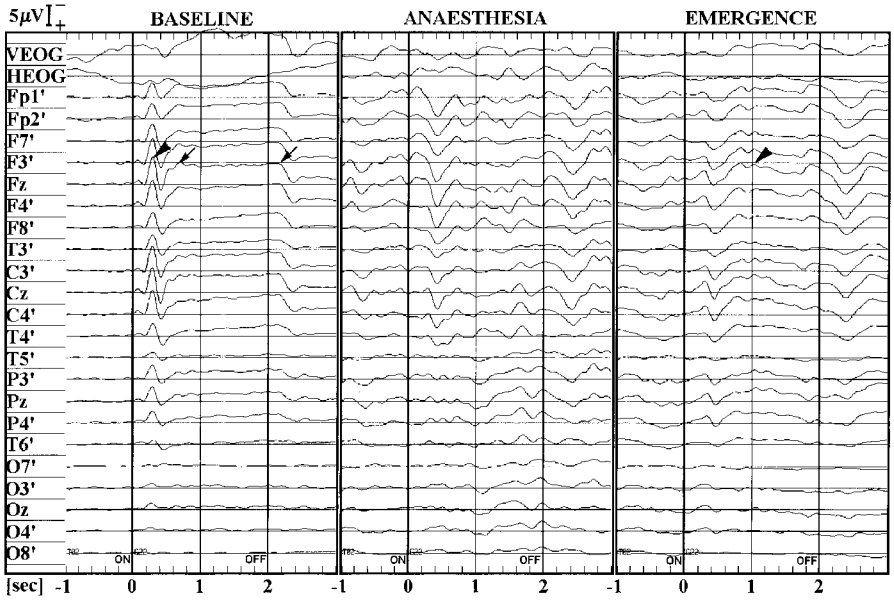

Figure 1. Grand mean auditory evoked potentials during awake baseline, anesthesia, and emergence from anesthesia (ON = stimulus onset; OFF = stimulus offset). In the baseline condition, a transient negative potential with a latency around 140 ms and a maximum amplitude at electrode Fz (arrowhead) is followed by a sustained direct current (DC) potential having a frontocentral topography and a maximum amplitude at electrode Fz (onset and offset of the DC component are marked by two arrows). After termination of stimulus presentation (OFF), return of the DC amplitude to the prestimulus amplitude level can be observed. No sustained component is observable during anesthesia. However, the DC component reappears during emergence of anesthesia. Although having a slightly lower amplitude and showing a less sharp onset and offset compared with baseline, it shows a similar topography as during baseline, and its maximum amplitude is also at electrode Fz (arrowhead).

Table 1. Hemodynamic Variables and Peripheral Oxygen Saturation (Spo_2) in Volunteers Anesthetized with Propofol or Methohexital

Variable	0 min[a]	5 min	10 min	15 min	20 min	End[b]
Systolic arterial pressure (mm Hg)						
Propofol	129 ± 5	112 ± 4	101 ± 2*	100 ± 2†	98 ± 3†	95 ± 3
Methohexital	127 ± 6	116 ± 5	111 ± 5	112 ± 3	113 ± 3	104 ± 3
Mean arterial pressure (mm Hg)						
Propofol	81 ± 3	71 ± 3	66 ± 2*	61 ± 2*	61 ± 4	59 ± 1
Methohexital	84 ± 4	81 ± 5	76 ± 3	73 ± 3	72 ± 5	66 ± 6
Diastolic arterial pressure (mm Hg)						
Propofol	63 ± 3	51 ± 3	49 ± 5	41 ± 2†	46 ± 5	49 ± 2
Methohexital	61 ± 3	62 ± 4	58 ± 2	55 ± 4	56 ± 5	49 ± 9
Heart rate (bpm)						
Propofol	72 ± 4	78 ± 4†	75 ± 4†	72 ± 4	68 ± 3	68 ± 3
Methohexital	81 ± 7	101 ± 4	98 ± 5	82 ± 5	80 ± 7	73 ± 6
Spo_2 (%)						
Propofol	99 ± 1	99 ± 1	99 ± 1	98 ± 1	98 ± 1	96 ± 1
Methohexital	98 ± 1	99 ± 1	99 ± 1	97 ± 1	97 ± 1	96 ± 1

[a] 0 min = before anesthesia.
[b] End = end of emergence.
* $P < 0.05$ between groups.
† $P < 0.01$ between groups.

sites. During anesthesia, no such response was observed. It reappeared, however, during emergence from anesthesia. Although having a slightly lower amplitude and showing a less sharp onset and offset compared with DC-AEPs during baseline, this component showed a topography almost identical to the one during baseline (Fig. 1 and 2), and its maximum amplitude was also located at electrode Fz.

The first ANOVA compared anesthesia and baseline. It yielded significant main effects STATE ($F_{1,14}$ = 6.18, $P = 0.026$, $\eta^2 = 0.31$) and LOCATION ($F_{21,294}$ = 3.42, $\epsilon = .12$, $P = 0.021$, $\eta^2 = 0.20$) and a significant interaction STATE × LOCATION ($F_{21,294} = 8.03$, ϵ = 0.12, $P = 0.001$, $\eta^2 = 0.36$). There was no effect of GROUP, because all F tests that included this factor were far from being significant. Thereafter, we examined whether DC-AEPs during emergence were different from those during anesthesia. A significant interaction STATE × LOCATION ($F_{21,349} = 3.18$, $\epsilon = .14$, $P = 0.03$, $\eta^2 = 0.19$) indicated that this was the case. Again, every F test that included the factor GROUP but also the main effects STATE ($P = 0.181$) and LOCATION ($P = 0.240$) were not significant. The third univariate ANOVA compared baseline and emergence from anesthesia. The only significance was observed for the main effect LOCATION ($F_{21,394} = 16.03$, $\epsilon = 0.14$, $P < 0.001$, $\eta^2 = 0.53$).

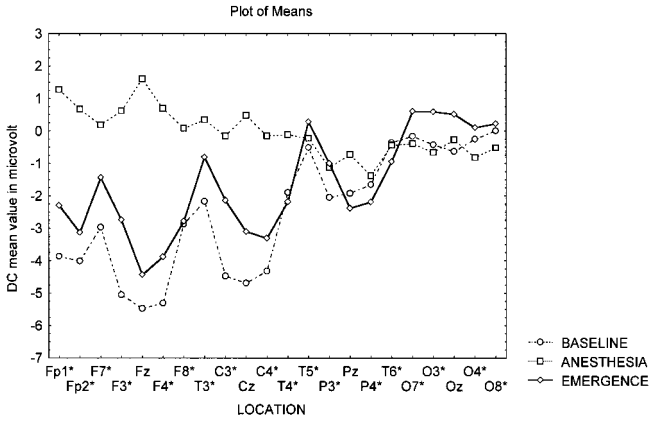

Figure 2. Grand mean plot of the direct current (DC) mean values used for statistical analysis. Plotted are the mean DC amplitude per electrode of the 16 subjects in the interval 500 ms until 2 s after stimulus presentation. Both amplitudes and topographical line pattern of anesthesia are clearly different from the other two conditions. Despite negative amplitudes being generally lower, the topographical line pattern of emergence is almost identical to baseline, with maximal amplitudes at fronto-medial electrodes and almost no activity at occipital electrodes.

We examined whether the differences between conditions could also be demonstrated when only a small part of the 22 electrodes was used. The linear contrast of F3′F4′Fz (anesthesia) versus F3′F4′Fz (baseline) was significant with $F_{1,14} = 11.38$ and $P = 0.005$. With the same electrode configuration, anesthesia and emergence from anesthesia were compared. Again, a significant difference was obtained ($F_{1,14} = 5.58$, $P = 0.033$). Finally, the same linear contrast was applied on data acquired during baseline and emergence from anesthesia. With $F_{1,14} = 1.13$ and $P = 0.306$, the two conditions did not differ. As expected, none of the occipital linear contrasts (electrode configuration O7′ to O8′, see Methods) were significant (baseline/anesthesia, $P = 0.719$; anesthesia/emergence, $P = 0.252$; baseline/emergence, $P = 0.179$). In summary, the linear contrasts confirmed the omnibus (ANOVA) tests.

By using the values at Fz, F3′, and F4′ as predictors, discrimination among the three different conditions was evaluated with stepwise forward discriminant analysis. Analyzing baseline and anesthesia, 36% of variance (Wilk's $\lambda = 0.64$) was explained by the discriminant function equation based on F3′ alone (the other predictors did not qualify for the analysis, most likely because of suppression effects), yielding significant discrimination ($P < 0.001$) with classification being correct in 88% of the cases. Only cases belonging to anesthesia showed misclassification, whereas 100% of the baseline cases were classified correctly. Discrimination between baseline and emergence was not possible (none of the predictors showed sufficient discriminability), whereas the third analysis (anesthesia vs emergence) was successful again ($P = 0.008$), with 21% explained variance by predictor Fz alone (Wilk's $\lambda = 0.79$; F3′ and F4′ did not qualify for the discriminant function). In this analysis, 75% of the anesthesia and 63% of emergence cases were classified correctly, resulting in an overall hit rate of 69%. Although the correct classification rates of the two successful analyses are clearly above chance level, their percentages of explained variance are small, pointing to discriminant variables other than those acquired in our experiment. We were not able to perform cross-validation because of the small sample size. Nevertheless, the analysis revealed that—apart from the result that anesthesia and baseline are clearly separable—discrimination of emergence and anesthesia is also possible and that in this analysis, data recorded during anesthesia are classified slightly better than those of emergence.

Discussion

AEPs are classically divided, on the basis of their latency, into first, fast, middle, slow, and late components (13). Sustained potentials of single polarity may be discriminated from these transient, or AC, components when longer acoustic stimulation is used (14). Most studies on the relationship of AEP components to anesthesia in humans have focused on transient components. Small increases in the latencies of waves III and V of the fast (brainstem) auditory evoked response have repeatedly been observed (15,16). However, these early components seem to be largely unaffected by most anesthetics (17). Both increases in latencies and decreases of peak-to-peak amplitudes of the middle-latency components Na, Pa, Nb, and Pb have been observed with different anesthetics (18–20). During sufentanil anesthesia, reduced latencies and amplitudes of P2 and disappearance of P3 were observed compared with the resting state (21), and it was reported that N1 and P3 could be recorded neither during anesthesia nor during emergence (22). Another approach is the recording of the 40-Hz auditory steady-state response (23). This response is attenuated in a concentration-dependent manner by isoflurane (24). One advantage of analyzing potentials evoked by sustained stimulation only is that they are less susceptible to short events (external as well as internal) that occur quite often during surgical operations (e.g., electrocoagulation, noise produced by alarm of the monitor or ventilator, etc.).

This is the first study that examines the DC component of evoked potential during anesthesia in humans. We investigated the effects of propofol- and methohexital-induced anesthesia on the DC auditory evoked response. During a preanesthetic baseline condition, we recorded highly plausible and reproducible DC potentials starting about 500 ms after stimulus

onset and dissolving shortly after stimulus offset. With regard to the time course and to the scalp distribution, this observation is in excellent agreement with other reports (11). During anesthesia, a DC potential could not be identified. This might be seen as an equivalent to the disappearance of the DC response in the anesthetized cat (2,3). Nevertheless, at the end of anesthesia when subjects were regaining consciousness, the DC potential reappeared. Although the mean amplitudes of this condition were slightly lower than those of the baseline condition, the topographical distribution of this condition is almost identical to the scalp potential pattern during baseline (Fig. 2) but clearly distinguishable from the pattern during anesthesia. The latter is important, because it demonstrates that the differences between anesthesia, baseline, and emergence are not solely caused by an unspecific difference in DC activity during anesthesia. The significant interactions of the location factor of the ANOVAs, together with the linear contrasts for the fronto-medial versus the occipital region, corroborate the interpretation that the effects we have observed were not caused by a global difference in cortical DC activity but by a location-specific difference, reflecting the presentation of auditory, but not visual, stimuli. Although differences in hemodynamic data were observed, the DC-AEP effects were not specific for the anesthetic used. However, our sample size was not large enough to allow definite conclusions on the interaction of anesthetic and cortical electrical activity. Nevertheless, if one follows the small-sample explanation, the effect size of the anesthetics must be small. If it were moderate or large, we would have obtained significance despite the small sample size. Hence, we can tentatively exclude that the effects seen were specific to the anesthetic.

Negative shifts as observed in the DC-AEPs during awake baseline are thought to be generated by excitatory postsynaptic potentials in the apical dendrites of the cortex (25). In addition to this neuronal generator, which is similarly responsible for the generation of transient or short-lasting evoked potentials, it is assumed that glial cells significantly contribute to DC potentials. These cells, which are omnipresent in cortical tissue, play an important role in the homeostasis of cortical tissue. Whenever prolonged neuronal activity is occurring, glial cells act as a local potassium buffer and seem to amplify and modify extracellular and resulting scalp DC potentials (26). The role of glial cells in the co-generation of DC potentials is, e.g., demonstrated by concurrent recordings from glial cells and from the cortical surface, which showed a similar activity time course of glial cells and the surface potential (27). Thus, we hypothesize that the suppression of DC activity during anesthesia is caused not only by a reduced input to apical dendrites and the resulting reduction in neural activity, but might additionally be caused by a suppression of glial functioning in the cortical tissue beneath the scalp electrodes, which might additionally suppress or reduce neural activity. This could be one reason for the high validity of DC-AEPs in the separation of the three states investigated in this study.

One problem with recording evoked potentials is that averaging is necessary. This results in the collection of data over longer (and possibly functionally different) periods of time. In the emergence condition, this has led to an overlap of trials immediately and up to about five minutes before regaining consciousness (this might be an explanation for the lower amplitudes in this condition). By selecting only 40 trials for each average, however, we think that we reduced this unavoidable overlap to a minimum. A further reduction of the number of trials would simply not have been acceptable with respect to signal-to-noise ratio. The percentages of explained variance in our ANOVAs and the hit rates in the discriminant analysis (approximately 90% for baseline vs anesthesia and 70% for anesthesia vs emergence) would need further improvement for clinical application. The rather large variability we observed might be caused by a number of physiological and nonphysiological influences. One of them, namely, the small but nevertheless existing overlap between averages, was already mentioned. Another important aspect is that the level of anesthesia showed large variability, as displayed by the anesthetic blood concentrations. This was a consequence of the short duration of anesthesia we applied in our protocol, introducing additional variability between and within subjects. A longer anesthetic period, displaying a more constant level of anesthesia, would certainly have allowed a better discrimination between anesthesia and emergence. However, because the character of our study was explorative, definite conclusions about these considerations are not yet possible. It should also be noted that in this study, we did not use a titration of anesthetics. The major aim was to determine the feasibility of DC potential recordings during anesthesia in humans and to test their potential effectiveness for separating three rather distinct states of consciousness. To investigate the clinical usefulness for the monitoring of anesthesia, future studies will have to demonstrate a dose-dependent relationship between anesthetic drug concentration and DC-AEPs and compare their effectiveness with that of other monitoring systems as, e.g., bispectral index.

As described in Methods, several aspects have to be considered to obtain stable recordings of DC or sustained evoked potential components. These include, e.g., gluing of electrodes to the scalp, a mandatory degassing of electrolyte to increase stability of recordings, skin scratching to reduce skin potentials and to minimize electrode impedance, and the use of a DC

amplifier with high-input impedance and baseline stability. This results in some extra time for electrode application and preparation when topographic recordings are made. However, it has to be noted that clinical application might not require a full scalp montage of electrodes. As the linear contrasts have shown, the three fronto-medial electrodes are sufficient to achieve reliable separation between the three conditions investigated in this study. If only such few electrodes are used, this will not result in too much extra time for electrode application and skin preparation. Another challenge during perioperative recordings is that mechanical pressure on electrodes, as well as movements of the head, can produce quite serious artifacts. However, this is problematic not only for DC, but also for AC EEG recordings. Thus, the technical challenges in obtaining reliable perioperative DC recordings are similar to those for AC EEG recordings, except for the requirement of a highly stable DC amplifier with high-input impedance. Such amplifiers are now becoming commercially available (e.g., Neuroscan, Sterling, VA), and this might trigger the more widespread use of this method in clinical research and application.

It should also be considered that all of our evidence is statistical, because it is based on conclusions for the whole sample. Although the mean pattern is clearly reflected when one inspects the data of single subjects, we observed considerable variability between subjects. Nevertheless, our statistical analyses show that this variability is still smaller than the differences caused by the three different conditions. In conclusion, effects similar to those reported in animal studies of anesthetics on the DC-AEP could be observed in anesthetized humans. The results of our exploratory study demonstrate the potential usefulness of DC-AEPs for the monitoring of cortical function during anesthesia in humans. Further studies focusing on dose-dependent modulation of DC-AEPs and comparing the method with other monitoring devices will have to show whether the method is valid enough to be used in the monitoring of depth of anesthesia.

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