Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflurane

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Significant changes in topographic quantitative EEG (QEEG) features were documented during induction and emergence from anaesthesia induced by the systematic administration of sevoflurane and propofol in combination with remifentanil. The goal was to identify those changes that were sensitive to alterations in the state of consciousness but independent of anaesthetic protocol. Healthy paid volunteers were anaesthetized and reawakened using propofol/remifentanil and sevoflurane/remifentanil, administered in graded steps while the level of arousal was measured. Alterations in the level of arousal were accompanied by significant QEEG changes, many of which were consistent across anaesthetic protocols. Light sedation was accompanied by decreased posterior alpha and increased frontal/central beta power. Frontal power predominance increased with deeper sedation, involving alpha and, to a lesser extent, delta and theta power. With loss of consciousness, delta and theta power increased further in anterior regions and also spread to posterior regions. These changes reversed with return to consciousness.

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Several attempts have been made to describe anaesthesia-induced topographic changes in the EEG. These studies relied upon conventional EEG with visual interpretation1, 2 despite problems with EEG variability across patients and anaesthetics and the subjectivity of conventional EEG interpretation.3, 4 Anaesthesia induction was associated with a frontal increase in beta activity that spread to more posterior regions as sedation level was increased and consciousness was lost. Delta activity appeared in posterior regions and migrated towards frontal regions. These observations of anaesthesia-induced EEG changes were summarized by the term ‘frontal predominance’.5 Frontal/central increases in beta1 (12.75–20.0 Hz) activity have been proposed as the most reliable indicators of sedation with propofol, although beta2 (20.25–30.0 Hz) and alpha2 (10.25–12.5 Hz) activity also increased.6 Isoflurane/N2O inhalation was shown to result in frontal alpha dominance.7 However, none of these reports enabled direct comparisons across different anaesthetics, all used subjective rather than objective evaluation of EEG changes, and all failed to take account of individual EEG variability before the initiation of anaesthesia.

Improvements in quantitative EEG (QEEG) techniques have included computer extraction of quantitative EEG measures evaluated statistically using standard scores relative to the EEG obtained from a database of normal awake adults (i.e. neurometrics).8 The present study examined changes in QEEG standard scores associated with the loss and return of consciousness in healthy normal volunteers who were anaesthetized with a technique using i.v. propofol and one using inhalation of sevoflurane. The purpose was to identify those QEEG variables that reliably
reflected sedation level and the loss and return of conscious awareness by showing similar changes during the two anaesthetic protocols.

**Subjects and methods**

**Subject population**

The subjects were eight male and eight female ASA I paid volunteers between the ages of 20 and 40 yr (mean 30.3, SD 6.3), tested with two different anaesthesia protocols (the order was randomized), with at least 30 days between sessions. This study was approved by the Committee on Studies Involving Human Beings and written informed consent was obtained from each volunteer. All 16 volunteers completed the propofol protocol and 14 completed the sevoflurane protocol (two volunteers withdrew for personal reasons unrelated to the study).

**Anaesthetic protocols**

Both anaesthetic protocols were designed to parallel those in current clinical use at Brigham and Women’s Hospital and to minimize risk and discomfort within our volunteer population. Premedication was either fentanyl 50 µg plus midazolam 1 mg or fentanyl 50 µg plus saline (randomized). An additional 50 µg of fentanyl was given to one volunteer during propofol administration because of discomfort associated with the placement of an arterial sampling line for obtaining propofol serum concentrations. Blood pressure, ECG, peripheral arterial oxygen saturation and axillary temperature were monitored. Anaesthesia was induced using age-corrected 0.1 minimal alveolar concentration (MAC=end-tidal concentration at which 50% of the population will move to a painful stimulus) steps for sevoflurane [based on the package insert for Ultane (sevoflurane); Abbott Laboratories, Chicago, IL, USA], or equivalent increments for propofol [MEC$_{50}$=minimal effect-site concentration at which 50% of the population will move to a painful stimulus (6 µg ml$^{-1}$)]$^9$ in combination with an infusion of remifentanil set to achieve a target effect-site concentration of 0.5 ng/ml (a concentration known to minimize chest wall rigidity). Propofol and remifentanil were administered at targeted effect-site concentration steps using the StanPump (developed by S. Schafer, from whom it is available free of charge) computer-assisted infusion technique. (The pharmacokinetic profiles for propofol and remifentanil used were from Gebts E, Camu F, Cockshoff ID, et al. Disposition of propofol administration as constant rate intravenous infusions in humans. Anesth Analg 1987; 66: 1256–63 and Minto CF, Schnider TW, Egan TD, et al. The influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 1997; 86: 10–23 respectively.) Sevoflurane was administered with end-tidal concentrations monitored with a calibrated Ohmeda gas concentration monitor (Datex Ohmeda – Anesthetic gas monitor, Instrumentarium, Helsinki, Finland) in steps of 0.1 MAC using an overpressure technique (Hewlett-Packard 58 gas chromatograph with flame ionization detection, Agilent, Inc., USA; Harvard Medical School).

Anaesthesia was administered in incremental 0.1 MAC/MEC$_{50}$ equivalent steps in both protocols until loss of consciousness (LOC), and then increased to 0.7, 1.0 and 1.4 MAC/MEC$_{50}$. Once at 1.4 MAC/MEC$_{50}$, the target concentration of remifentanil was increased to 6.75 ng ml$^{-1}$, succinylcholine 1.5 mg kg$^{-1}$ and laryngeal lidocaine spray 100 mg were administered, and the trachea was intubated. The remifentanil target concentration was then reduced to 1.75 ng ml$^{-1}$ and the anaesthetic concentration was reduced in steps of 0.1 MAC/MEC$_{50}$ until the return of consciousness (ROC). After each targeted hypnotic drug concentration had been achieved, the new concentration was maintained for an additional 8–10 min while the EEG and a measurement of level of arousal were obtained. LOC and ROC were defined using the measure of level of sedation described below.

In the propofol protocol, propofol and remifentanil concentrations were obtained at LOC, 0.7 and 1.0 MEC$_{50}$, and ROC, from blood samples acquired from a radial artery catheter for comparison with targeted plasma concentrations. Propofol plasma concentrations were based upon duplicate 2 ml samples using gas chromatographic separation with a 15 m × 0.53 mm internal diameter (ID) column with 1.5 µm 10B-5 film thickness and flame ionization, and accuracy was assessed using plasma samples with known drug concentrations. Remifentanil concentration was determined in duplicate citric acid-preserved arterial samples, with remifentanil separated using a 4 m × 0.25 mm ID DB-5 column with 0.75 cm film thickness, and high-resolution mass spectrometry with selective ion monitoring. Remifentanil concentrations of 0.026–8 ng µl$^{-1}$ served as controls (mass spectrometer Uh70-V5H; Fison Instruments Inc., Rochester, MN, USA).

**Measurement of level of sedation**

After each targeted effect-site concentration had been achieved, the volunteer’s level of sedation was measured immediately after the EEG had been collected, using a modification of the responsiveness component of the Observers Assessment of Alertness and Sedation scale (OAAS).$^{10}$ $^{11}$ The following scoring system was used: 5=responds readily to command spoken in normal tone; 4=lethargic response to command spoken in normal tone; 3=lethargic response to command spoken loudly and repeatedly; 2=displays an appropriate response to command only after a loud verbal command and a mildly painful stimulus (train of four); 1=displays an appropriate response to command only after a loud verbal command and a moderately painful stimulus (50 Hz electrical stimulation for 1 s); 0=no response to verbal command with painful
stimulus. Both painful electrical stimuli were applied to the wrist using a constant current stimulator set at 40 mA. Loss of the eyelash response was always found before checking a volunteer’s sedation level below an OAAS score of 3. Using this scale, a score of less than 3 but greater than 0 represents the ability to respond appropriately to a loudly spoken verbal command accompanied by a painful electrical stimulus. In this situation it was important to differentiate an appropriate response to command from a response representing a pain-induced aversive or flexion reflex. An appropriate response to command after a painful stimulus was considered to result from a return to consciousness after it was lost. Failure to show an aversive movement to a loudly spoken verbal command with concurrent painful stimulation represented an anaesthetic depth that was equal to or greater than MAC/MEC50. In all analyses presented below, the LOC end-point used was a score of 0.

EEG acquisition

EEG was collected before premedication, after premedication and at each step of the protocol during and after equilibration at each drug concentration, as determined by the StanPump readout. All EEG data were collected with the eyes closed and the volunteer lying comfortably in a holding area or in an operating theatre suite. Gold cup electrodes filled with collodion were placed over 19 standard regions defined by the international 10/20 system, referenced to linked ears. All electrode impedance levels were kept below 5000 Ω. The EEG amplifiers had an acquisition bandpass from 0.5 to 100 Hz (3 dB points) with a 60 Hz notch filter. Differential recording channels were used to monitor eye movement artefact, movement artefact and the ECG. One minute of artefact-free EEG (twenty-four 2.5 s epochs) was selected by visual editing of the continuous EEG that was recorded after equilibration had been reached for each stage of the protocol. The artefact-free EEG was converted from the time to the frequency domain using a fast Fourier transform (FFT). This paper will concentrate on one of the protocols. The artefact-free EEG was converted from selected by visual editing of the continuous EEG that was minute of artefact-free EEG (twenty-four 2.5 s epochs) was alpha (7.5±12.5 Hz), beta (12.5±25.0 Hz) and total (1.5±25.0 Hz) frequency bands.

Statistical methods

Anaesthetic delivery accuracy was evaluated using Pearson product moment correlations between the target and actual drug concentrations at each stage of the protocol. QEEG data analyses were accomplished as follows. Each QEEG feature was expressed as a Z-score (standard score) relative to the mean and standard deviation of the same QEEG feature obtained from an age-regressed, normalized data base of 250 normal awake adults. The Z-scores for absolute power features collected in the non-medicated, baseline state were compared with those obtained after premedication, and during induction and emergence separately for sevoﬂurane and propofol anaesthesia. QEEG absolute power differences between sevoﬂurane and propofol during induction and emergence from anaesthesia were also examined, as were differences as a function of remifentanil concentration. The same statistical procedures were applied for all comparisons. One-way repeated measures analyses of variance (ANOVA)s were calculated for each of the 19 monopolar leads within each frequency band. The F values and the averaged Z-scores associated with these comparisons are displayed in Figs 2–4. The colour-coding in Fig. 2 is proportional to the mean Z-score of each averaged sample. The significance of the mean Z-scores in these maps can be determined by taking into account the square root of the sample size. Thus, the 0.0001 level of significance for the propofol group with n=16 is 1.11 (4.42/4), and for the sevoﬂurane group with n=14 it is 1.14 (4.42/3.74). Because multiple analyses of variance were calculated, rigorous criteria for significance were used to interpret each ANOVA. Only P values less than or equal to the 0.001 level were considered significant.

Results

Predicted vs actual anaesthetic concentrations

The Pearson correlation between predicted and measured propofol plasma concentration was 0.89, between predicted and measured remifentanil plasma concentration 0.79, and between targeted and measured end-tidal expired sevoﬂurane concentration 0.97, with P<0.001 for all three correlations. Figures 1A and B show these relationships for propofol and sevoﬂurane. The mean plasma concentrations of propofol were 3.44 (SD 1.5) and 2.55 (0.8) μg ml⁻¹ at LOC and ROC respectively. The mean StanPump predicted propofol effect-site concentrations were 2.52 (1.1) and 1.96 (0.5) μg ml⁻¹ at LOC and ROC. End-tidal expired sevoﬂurane concentrations were 0.43 (0.17) and 0.26 (0.07) MAC at LOC and ROC. The mean measured plasma concentration of remifentanil was 0.48 (0.16) ng ml⁻¹ at LOC and 1.4 (0.4) ng ml⁻¹ at ROC.

Arousal level during LOC and ROC

In the majority of volunteers, changes in sedation level during induction were discontinuous, not passing through all steps in the OAAS scale. In most volunteers, failure to respond to a loud verbal command was the induction end-point, and subsequent painful stimulation was unable to re-establish consciousness. However, 3/14 sevoﬂurane and 7/16 propofol subjects (total=33.3%) were not aroused to loud verbal commands or train-of-four stimulation but regained consciousness after 50 Hz painful stimuli. During emergence in both protocols, ROC was elicited initially by a verbal command alone, 4/15 sevoﬂurane and 2/16 propofol volunteers showing an appropriate response initially to a
loud verbal command after either mildly or moderately painful stimulation.

**Baseline QEEG and premedication effects**

None of the average premedication baseline absolute power Z-scores was significantly different from the normative values obtained from the normal awake adult database described previously. Premedication with fentanyl or fentanyl plus midazolam had no significant effect upon the QEEG. None of the ANOVA F values comparing the baseline non-medicated with the premedicated QEEG reached statistical significance at even the 0.05 level.

**QEEG and remifentanil concentration**

Mean remifentanil concentrations were greater during emergence from anaesthesia than during induction (0.5 vs 1.75 ng ml⁻¹). This was of little consequence for the QEEG changes associated with induction and emergence described below. ANOVAs calculated at equivalent propofol/sevoflurane target concentrations but different remifentanil concentrations obtained during induction and emergence did not reach statistical significance (all P values >0.05).

**QEEG changes during induction**

In order to minimize drug concentration effects on the QEEG while maximizing the relationship between QEEG changes and behavioural changes in responsiveness, QEEGs were averaged across subjects relative to the LOC end-point of OAAS=0 rather than at specific drug concentrations. When QEEGs were averaged in this manner, the global patterns of absolute power changes seen during induction were the same for sevoflurane and propofol. However, the magnitude and degree of statistical significance of these effects differed, especially during light sedation (Figs 2A and 2C and 4A and 4C). Light sedation (2 pre-LOC; measured at two 0.1 MAC/MEC₅₀ concentration increments before OAAS=0) resulted in increased frontal/central beta and total power. Deeper sedation (1 pre-LOC: one 0.1 MAC/MEC₅₀ concentration increment before OAAS=0) resulted in further increases in frontal/central beta and delta activity, beginning in frontal regions and propagating to posterior regions. LOC (OAAS=0) was accompanied by increased frontal predominance within every frequency band for propofol and across delta, alpha and beta, but not theta, for sevoflurane. Frontal predominance in total absolute power increased as induction progressed to LOC. No differences in the QEEG changes were observed between the left and right hemispheres.

**Anaesthetic-specific effects during induction**

Figure 3A presents ANOVA F values comparing absolute power levels for the sevoflurane vs propofol groups at each targeted step during induction. In the deeply sedated state and at LOC, ANOVAs suggested that propofol tended to cause a greater frontal alpha predominance than did sevoflurane. Although not shown, frontal alpha predominance continued to increase with sevoflurane but not with propofol, at the higher concentrations studied after LOC (0.7 and 1.0 MAC).

**QEEG changes associated with emergence**

Differences between the baseline absolute power QEEG measures, the two 0.1 MAC/MEC₅₀ concentration incre-
ments before ROC and at ROC are shown in Figures 2B and D and 4B and D. The pattern of QEEG changes observed during emergence is a reversal of those observed during induction. The changes were the same for sevoflurane and propofol, although once again their magnitude and degree of statistical significance differed. Frontal predominance in all frequency bands diminished as conscious awareness approached. ROC was associated with further decreases in delta and beta frontal predominance. The QEEG observed two 0.1 MAC/MEC<sub>50</sub> concentration increments before emergence was similar to the QEEG seen at LOC, with the exception that frontal predominance was increased. QEEG changes just before ROC also showed reduced frontal predominance, which was still prominent in beta activity. The QEEG observed at ROC resembled that seen one 0.1 MAC/MEC<sub>50</sub> concentration increment before ROC rather than the baseline QEEG. These QEEG changes were independent of anaesthetic concentrations as LOC (sevoflurane, 0.43 MAC; propofol, 0.41 MEC50) occurred at greater anaesthetic concentrations than did ROC (sevoflurane, 0.26 MAC; propofol, 0.33 MEC50). There were no indications of differential left vs right hemispheric QEEG changes associated with emergence from anaesthesia.

Anaesthetic-specific effects during emergence
Comparisons between the sevoflurane and propofol groups during emergence indicated a faster return towards baseline QEEG values for sevoflurane compared with propofol (Fig. 3B). Two 0.1 MAC/MEC<sub>50</sub> concentration increments before ROC, the sevoflurane volunteers showed significantly greater posterior beta absolute power, whereas the propofol group showed increased frontal delta and theta absolute power ($P<0.001$). At one 0.1 MAC/MEC<sub>50</sub> concentration increment before ROC, the propofol group showed greater delta, theta and alpha frontal predominance. None of these differences was observed at ROC.

Discussion
QEEG absolute power values, Z-score-transformed relative to an age-appropriate database of normal awake individuals,
were used to document topographic EEG changes associated with stepwise increases and decreases in anaesthetic concentration that produced the loss and return of consciousness. The QEEG technique used takes into account EEG variability due to age and pre-existing brain pathology and appropriately transforms EEG variables to meet the assumptions of parametric statistical procedures. This technique has shown high test-retest reliability and the normal QEEG database used as a reference group has been repeatedly replicated and shown to be free of ethnic and cultural bias. Both of these findings were confirmed in the present study. The awake, non-medicated baseline QEEG evaluations did not differ statistically from the normal adult population values. The use of this QEEG technique may explain the lack of hemispheric effects found in this study, contrary to the hemispheric EEG differences reported by Kisimoto and colleagues during propofol administration. It is possible that hemispheric differences reported in their study represent patient population sampling effects.

The QEEG changes observed during induction and emergence during the propofol and sevoflurane protocols can reasonably be considered to be specific for alterations in sedation level, and substantially independent of anaesthetic type and concentration. The QEEG analyses were centred on clinically defined end-points (LOC and ROC), times that drug concentrations differed both within individuals across anaesthetics and between individuals within anaesthetics. Only QEEG changes which were common to sevoflurane and propofol administration were considered to reflect changes in arousal level. The anaesthetic-independent QEEG changes during light sedation included loss of the posterior alpha predominance seen in the normal relaxed, eyes-closed EEG, accompanied by a shift towards frontal EEG predominance. This occurred initially within the beta range, with deeper levels of sedation involving alpha activity, and at still deeper levels the delta and theta frequency bands. At LOC, frontal predominance was maximal in the alpha and beta bands and continued to increase for slow waves that also spread to more posterior regions. QEEG changes associated with light levels of sedation were equivalent for sevoflurane and propofol. Anaesthetic-specific effects were observed immediately before and at LOC. Propofol administration caused a greater increase in frontal alpha predominance at LOC than did sevoflurane. However, as sevoflurane concentrations were increased beyond those necessary to cause LOC, the differences disappeared.

Anaesthetic-independent QEEG changes associated with ROC were a gradual reversal of those which occurred at LOC, with the proviso that the QEEG and level of responsiveness measured at ROC resembles that seen before LOC rather than the awake, premedicated baseline state. This reflects the frequently made observation that patients regain conscious awareness at depressed levels of arousal, whereas just before induction they are alert and anxious, and readily respond to simple verbal commands. Emergence was preceded by a generalized decrease in delta and theta absolute power with a concurrent reduction in frontal predominance within these frequency bands. A decrease in alpha and an increase in beta frontal predominance followed. ROC was associated with a further reduction of frontal predominance that remained present in the beta frequency band only. Anaesthetic-specific QEEG changes associated with ROC were similar but opposite to the anaesthetic-specific effects present at LOC. The loss of power in the delta and theta bands and the subsequent decrease and loss of frontal predominance in all bands

Fig. 3 Topographic maps of analysis of variance $F'$ values calculated on each of the 19 monopolar regions on Z-score absolute power values for the total, delta, theta, alpha and beta frequency bands. The rows correspond to comparisons between the propofol (A) and sevoflurane (B) groups for baseline premedicated QEEGs, the two 0.1 MAC/MEC$_{50}$ concentration increments preceding LOC, LOC, the two 0.1 MAC/MEC$_{50}$ concentration increments preceding ROC, and ROC. The $F'$ values calculated had 1 and 29 degrees of freedom with $F'$ values of 13.4 significant at the 0.001 level (see arrow on the scale).
occurred to a greater extent with sevoflurane before ROC than it did with propofol. It should be noted that both the magnitude and the statistical significance of the anaesthetic-independent effects shown in Fig. 4 (change as a function of OAAS score) are two to four times greater than the anaesthetic-specific effects shown in Fig. 3 (change as a function of anaesthetic type).

Similar and reversible LOC/ROC QEEG changes occurred despite the fact that remifentanil concentrations were greater during the recovery from anaesthesia than during induction, as defined in the protocols used. Remifentanil concentration had minimal effect upon the QEEG despite the possible influence of remifentanil concentration upon the propofol and sevoflurane concentration differences observed between LOC and ROC. These concentration differences may also be explained by a hysteresis effect.25

The finding that invariant QEEG changes occur during induction and emergence from two different anaesthetic regimens supports the notion that QEEG can be used to monitor anaesthetic delivery. Indeed, there are several systems currently available on the market for this purpose. The current research findings have implications for determining the types of QEEG features that may be important for use in an anaesthesia monitoring system. Further, the topographic nature of the invariant QEEG changes observed suggests that anterior/posterior EEG recording derivations may be important to optimize the sensitivity of such a device.

Knowledge about the generators of each EEG frequency band can provide information relevant to the development of hypotheses about the neuroanatomical, neurophysiological and neurochemical mechanisms underlying the sedative and hypnotic effects shared by sevoflurane and propofol. The EEG power spectrum is mediated by an anatomically complex and diverse system that involves brainstem, thalamic, hippocampal and cortical/cortical neuronal pathways that use all known neurotransmitters. Specific portions of this system are involved in the generation of EEG within each frequency band, the interaction of activity among these generators being responsible for the frequency distribution of the EEG.22 26 27 Both propofol and sevoflurane anaesthesia would appear to affect each of these systems. As sedation levels increase, the posterior regions show a decrease in alpha activity, and an initial excitation of the frontal cortical regions becomes manifest. With deepening levels of sedation, the prominence of the frontal changes...
increases from midline frontal to frontal/polar regions. With loss of consciousness, slow-wave activity (delta and/or theta) becomes more prominent, with a simultaneous decrease in alpha and beta activity. This may represent a decrease in cortical/cortical generator activity, with a shift towards control by the thalamocortical and hippocampal/septal generators of delta and theta activity. The return of consciousness is associated with a reversal of these effects. A more detailed exposition of the neurophysiology of consciousness and its relationship to QEEG has been published recently.\textsuperscript{28} While the above descriptions are speculative, they may serve to highlight the importance of further study of the neurophysiological mechanisms involved in the generation of the EEG to help identify the common and unique mechanisms affected by various sedative and hypnotic agents.

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