Power Spectrum Correlates of Changes in Consciousness during Anesthetic Induction with Enflurane

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In order to correlate electroencephalogram (EEG) changes during anesthetic induction with level of consciousness, four-channel parasagittal EEG recordings were made during anesthetic induction with enflurane and enflurane–nitrous oxide in oxygen. The EEG was quantitated using power spectrum analysis. Significant EEG changes were identified during all anesthetic inductions; however, the frequency of occurrence of change was significant only during the development of amnesia (15 of 20 subjects, \( P = 0.04 \)). The nature of the EEG changes at this time was agent-specific (\( P < 0.05 \) by chi-square), with high-frequency changes evident in the enflurane group and shifts in amplitude in the 8–12 Hz activity predominating in the nitrous oxide–enflurane group. Anterior dominance could not be documented as a correlate of amnesia or unresponsiveness. The identification of such EEG changes may be valuable in assessing anesthetic depth, but other effects, such as the response of the EEG to surgical stimulation, must be determined before the results are clinically applicable. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: enflurane. Brain: electroencephalogram. Monitoring: electroencephalography.)

Although numerous studies have been performed on the electroencephalogram (EEG) under anesthesia, few of these have concentrated on the EEG changes under subanesthetic concentrations. When such studies have been performed, they have emphasized the relationship between the EEG and the anesthetic concentration, or have utilized agents not commonly used any longer. Other studies, which have assessed functional state, have omitted the spontaneous EEG entirely, investigating only the effects of the anesthetic on the evoked potential. Such omissions increase the difficulty faced by anesthesiologists who wish to apply modern EEG technology to lightly anesthetized patients. Further aggravating this problem has been the lack of quantitative techniques capable of identifying small changes in the EEG. Accordingly, this study of EEG changes during the induction of anesthesia was undertaken with three goals in mind: 1) to develop quantitative analysis techniques that are statistically valid and generally applicable to the EEG power spectrum; 2) to assess quantitatively EEG changes in relation to the functional depression of the central nervous system during enflurane anesthesia; and 3) to compare these EEG patterns with the EEG recorded at comparable levels of functional depression when nitrous oxide and enflurane are used for anesthetic induction.

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Materials and Methods

Twenty healthy patients (ten men) participated in this study, which was approved by the Committee on Studies Involving Human Beings. Informed consent was obtained following the routine preoperative visit.

Patients were given no premedication. After arrival in the operating room, an intravenous catheter, blood pressure cuff, and electrocardiogram leads were placed for monitoring. Silver/silver-chloride disc or platinum needle electrodes were then placed for EEG recording. These recordings were performed using a four-channel right parasagittal common-reference electrode montage of \( F_{Pz} \), \( F_4 \), \( C_4 \), \( P_4 \), to \( A_2 \), with \( A_1 \) as ground (fig. 1). The bandwidth of recording was 4 to 45 Hz (3 dB points).

Following the establishment of this monitoring, 3 mg curare was administered to limit fasciculation should succinylcholine be needed to treat excitement, and oxygen (6 l/min) was given by mask for 2 min so that the patient could accommodate to the uncommon sensation of breathing through the anesthesia circuit.

Anesthesia was then induced using one of two protocols. For induction with nitrous oxide–enflurane, 0.5% enflurane was added to 2 l/min oxygen and 4 l/min nitrous oxide. The inspired enflurane concentration was increased every 30 s by 0.5% until the subject failed to respond to a simple command. For induction with enflurane alone, a similar technique was used, but somewhat more individualization was found to be necessary in order to avoid excitement. Once again, the total flow was maintained at 6 l/min. The enflurane concentration was increased in 0.5% increments every 20–30 s unless the subject demonstrated breath-holding or other signs of airway irritability. With both protocols, following unresponsiveness, the inspired anesthetic concentration was maintained constant for 2 min, at which time the protocol terminated.

Anesthetic concentrations were not measured because under the conditions of the study neither the inspired nor end-tidal concentrations would be expected to reflect accurately the anesthetic concentrations in the brain. Following the study period, patients underwent surgical procedures and received barbiturates, narcotics, and additional enflurane and nitrous oxide as clinically indicated.

During the anesthetic induction, two sets of stimuli were given. Every 15 s, the subject was told the number of seconds since the beginning of the induction, providing a marker for the determination of the onset of amnesia. Every 30 s, subjects were told to open their eyes, allowing identification of unresponsiveness to a simple command. Postoperatively (6–24 h), subjects were asked for the last
number remembered as well as any other recollections about the induction period. If subjects recalled the number incorrectly (e.g., “130” when “135” was actually spoken), they were prompted to remember numbers that were spoken before the number in question and after it. When recall was present for the preceding numbers and absent for the subsequent ones, subjects were considered to be mnemonic for the incorrectly remembered number and amnesic for subsequent numbers.

Data analysis was performed by digitizing each channel of EEG recording at 128 Hz. Power spectrum analysis was then performed using 2-s epochs (256 data points/epoch), producing power spectra with a resolution of 0.5 Hz. These spectra were displayed using a density-modulated (DSA) display technique and were saved for subsequent analysis.

Based on the response of the subject, four periods were described for each subject. During oxygen breathing, a 30-s baseline period was identified. The 30 s prior to the last number remembered constituted the mnemonic period, while the 30-s period beginning with the first number not remembered formed the amnesic period. Thus, there was always a 15-s separation between the end of the mnemonic period and the start of the amnesic period. Finally, the 30-s period beginning at the time the subjects failed to open their eyes on command constituted the unresponsive period.

Prior to statistical analysis, the data were inspected for artifact, and epochs containing artifact were replaced with artifact-free epochs temporally adjacent to the periods being analyzed. No more than one-third of the data in any period was replaced. For the multichannel analysis of the shift in the dominance, the exclusion of any epoch from one channel resulted in its exclusion from all channels. The comparison of power spectra was performed using one-way analysis of variance with hierarchical classification. This technique identifies spectra as different when the sum of the variances of the power by channel (computed by frequency) is significantly less than the sum of the variances for all channels (computed by frequency). In other words, if the grouping by channel reduces the variance significantly, the spectra are different—not simply two samples drawn at random from the same population of data. Significance of a pattern of change in the population was tested using a binomial model.

Results

Amnesia occurred at a mean of 99 ± 7.1 (SEM) s after the beginning of induction. There was no significant difference in this time between the enflurane and the enflurane–nitrous oxide groups (97.5 ± 12.7 s and 100.5 ± 8.5 s, respectively). Unresponsiveness occurred 1 min later (160 ± 14.4 s); again, no differences existed between the two induction techniques (162 ± 13.5 s and 157.5 ± 27.2 s for enflurane and enflurane–nitrous oxide, respectively). The temporal difference between amnesia and unresponsiveness was significant at $P < 0.01$ by paired $t$ test.

Significant EEG changes were identified by analysis of variance during all of the inductions. When pairwise analysis between successive periods was used to identify the time at which these changes occurred, only the comparison of mnemonic and amnesic periods showed significant changes in a statistically significant percentage of the population. During this transition in mental function, 15 of the 20 subjects ($P = 0.04$) showed statistically significant changes in the EEG.

When anesthesia was induced using enflurane alone, statistically significant changes were observed between mnemonic and amnesic periods in seven out of ten cases. In six of these seven, increased high-frequency activity was notable, with the remaining case showing a diffuse reduction in amplitude at this time. The high-frequency activity was most prominent in the central or parietal channel (depending on the case) and was then noted to spread to the more frontal regions (fig. 2). In some cases, this high-frequency activity was evident in the unprocessed EEG (fig. 3) prior to the onset of amnesia; however, the low amplitude of this high-frequency activity precluded its identification in the processed recording. By the onset of amnesia, the high-frequency activity was quite notable, with the maximal amplitude still found in the central or parietal channels (fig. 4).

In the nitrous oxide–enflurane group, seven of the eight subjects who showed significant change between mnemonic and amnesic periods did not show high-frequency activity in the DSA. In these cases, changes in the frequency and amplitude of the alpha rhythm predominated, and only following the onset of unresponsiveness was high-frequency activity seen (fig. 5). Examination of the unprocessed EEG in these cases revealed low-amplitude, high-frequency activity in a predominantly central distribution that preceeded the development of amnesia.
FIG. 2. Frontal spread of high-frequency activity. Power spectra for one subject anesthetized with enflurane in oxygen are displayed. High-frequency activity is observed first in the central and parietal channels (C4 and P4), and only subsequently does it appear in the frontal (F3 and F4) channels. This subject also demonstrates slowing of her unusually prominent alpha rhythm during the development of the high-frequency activity. Unprocessed EEG from the points labeled "3" and "4" are shown in the corresponding figures.

FIG. 3. High-frequency activity before amnesia. Prior to the onset of amnesia, brief bursts of high-frequency activity are noted, predominantly in the more posterior leads of this montage. Because of its low amplitude and brief duration, this activity is not evident in the DSA (fig. 2).

FIG. 4. High-frequency activity during amnesia. Following the loss of memory, the EEG demonstrated more rhythmic and higher amplitude high-frequency activity than was seen previously.

The frequency of this activity is approximately 40 Hz; however, when examined in a more expanded time scale (fig. 6B), it is seen to lack rhythmicity, and thus failed to produce an identifiable pattern on the DSA, even when the bandwidth of the DSA was extended to 48 Hz. The difference in behavior of the power spectra between the enflurane and enflurane-nitrous oxide groups was significant (P < 0.05 by chi-square). It should also be noted that all subjects demonstrated high-frequency EEG changes during the 2 min following unresponsiveness.

Analysis of variance of the four EEG channels during the unresponsive period demonstrated significant differences between channels in only 12 of the 20 subjects (60%). Similar analysis performed on the EEG 2 min later demonstrated statistical differences among channels in 17 of the 20 subjects (85%, P < 0.01). Of these 17, two showed complex differences in the spectra among channels (fig. 7) and one showed posterior rather than anterior dominance.

Discussion

Many previous studies of the EEG during anesthesia1,5-7 equate anesthetic concentration with anesthetic depth, ignoring the well-known phenomenon of individual variation in sensitivity to pharmacologic agents. Such an approach increases the variation in the EEG for a given "anesthetic depth" because the subjects are not, in fact, at the same anesthetic depth. The use of mental state or specific level of autonomic function8,9 as an index of depth has two advantages. First, individual variability in response to anesthetic agent is eliminated, removing one source of statistical "noise" and allowing the identification of more subtle changes in the EEG. Second, this approach allows the study of transient conditions (such as the induction of anesthesia) in which end-tidal and brain concentrations do not have time to equilibrate. In such a situation (e.g., this study) the measurement of end-tidal anesthetic concentration is of no value and could even be misleading.
because the fundamental assumption for validity of these measurements is lacking. These advantages, however, may be offset by the loss of easily quantified, “hard” data.

In the absence of such data about anesthetic concentration, the similarity of the times of onset of amnesia and onset of unresponsiveness in the two groups of patients seems surprising. Patients in the nitrous oxide—enflurane group were receiving (on average) 0.5 MAC more anesthesia than those in the enflurane group. It is reasonable, therefore, to expect such patients to demonstrate amnesia and unresponsiveness more rapidly. The failure to demonstrate this expectation resulted from the variability of the duration of anesthetic induction prior to the onset of these identifiable functional states. Adam⁹ and Hosick et al.¹⁰ have previously demonstrated large individual variation in the response to subanesthetic concentrations of anesthetic agents. Respiratory rate and cardiac output are two additional factors that cannot be controlled during the anesthetic induction, but which strongly influence the rate of increase of alveolar concentration of an anesthetic agent.¹¹ Furthermore, patients who have been hyperventilating (due to anxiety) before the anesthetic induction may show compensatory hypoventilation as they become sedated from the induction agent and their respiratory centers revert to a more expected level of CO₂ responsiveness. As a result of these factors, one would expect a large variation in the time course of the induction from patient to patient and this in fact, was observed. The similarity of times to the onset of amnesia and unresponsiveness in the two groups is not in conflict with our understanding of the uptake of anesthetic agents, but indicates that individual variation has a greater effect on the time to loss of consciousness than the effect of an additional 0.5 MAC of nitrous oxide. Thus, by defining an-

![Graph](image)

**Fig. 5.** DSA for nitrous oxide and enflurane. The power spectra for a subject receiving enflurane and nitrous oxide are shown. Amnesia and unresponsiveness occurred before significant high-frequency activity was evident. The unprocessed EEG from the point labeled “6” is shown in figure 6.

![Graph](image)

**Fig. 6.** High-frequency activity due to nitrous oxide. In A, a segment of unprocessed EEG shows high-frequency, low-amplitude activity. The segment indicated by the bar is replotted in B. An expanded time scale (B) emphasizes the sporadic nature of this activity. This lack of rhythmicity precludes the identification of this activity in the DSA.
esthetie depth as a functional state, the variation due to uncontrolled variables is reduced, and comparison of the EEGs recorded at comparable anesthetic depth is assured, regardless of the duration of anesthetic induction.

The usefulness of the EEG for measuring anesthetic depth demands that there be easily recognizable electroencephalographic patterns associated with levels of anesthesia that cannot be identified by other respiratory or cardiovascular effects of the anesthetic. Previous studies of the EEG during enflurane anesthesia have emphasized the epileptogenic effects of the agent. Although these effects occur at clinically useful depths of anesthesia and are easily recognizable on the EEG, cardiovascular and respiratory depression are also present, providing other means of assessing anesthetic depth. At lighter anesthetic depths, the problem of assessing changes in the intraoperative EEG using conventional techniques makes it difficult to estimate changes in depth from the EEG.

Power spectrum analysis provides an effective way of processing the EEG for intraoperative monitoring; however, the assessment of patterns and changes in the power spectrum has been entirely an empirical process. By combining power spectrum analysis (to quantitate the EEG) with analysis of variance, it is possible to assess the significance of EEG changes in a more rigorous mathematical fashion. As a result, one may identify more subtle changes in the EEG with confidence. This is exemplified by figure 8, which shows the average power spectra for the amnesic and mnemonic periods in one patient. The differences between the spectra are relatively small, but are statistically significant.

Early work by Clark et al., and Bart et al., demonstrated that high-frequency activity occurs at low concentrations of enflurane, with slowing as anesthesia deepens. Our data corroborate this and demonstrate a strong association between the presence of such high-frequency activity and amnesia. Although similar high-frequency EEG changes have been associated with other sedatives, particularly the benzodiazepines and barbiturates, such changes are not necessarily associated with amnesia. A tendency for this activity to begin centrally and to progress in both anterior and posterior directions was also observed, although not in all subjects.

The addition of nitrous oxide to enflurane produced substantial differences in the pattern of EEG behavior seen. Small amounts of very high-frequency activity, similar to that described by Yamamura et al., was observed in the raw EEG but not in the DSA, and was not prominent frontally. These differences are most easily explained by differences in study design. In the previous study, fast oscillatory activity developed following 2 to 4 min of nitrous oxide inhalation; however, at the corresponding point in this study, patients were already receiving high concentrations of enflurane, and disturbance of the nitrous oxide oscillatory activity by enflurane could be expected. The inability to identify low-amplitude, high-frequency activity in the power spectrum in this study reemphasizes the mathematical characteristics of Fourier analysis, which averages power over the whole epoch and therefore results in a reduction in power when the
rhythmic activity occurs in bursts that are shorter than one epoch in duration. The shift in the frequency components of the alpha rhythm that was observed in the current study was similar to that seen by Henric et al., when only nitrous oxide was administered; however, some anxious patients show only weak alpha rhythms when the recording occurs immediately before surgery; thus, changes in the alpha rhythm may be unreliable indices of anesthetic depth.

Tinker et al. have previously reported the occurrence of a shift from posterior to frontal dominance at about 0.4 MAC and hypothesized that this represented the loss of awareness. Our analysis failed to confirm the association of frontal dominance and loss of awareness, and suggests that frontal dominance occurs at greater depth than unresponsiveness to a verbal command. Using analysis of variance, we were unable to identify significant differences in power among the channels in many patients when unresponsiveness occurred. This situation (which did not occur in Tinker’s animals) is the major explanation for the inability to demonstrate a statistically significant frequency of frontal dominance. The incidence of significant differences among the channels increased as anesthesia was deepened following unresponsiveness, and frontal dominance occurred frequently in the power spectra recorded 2 min following unresponsiveness. The continuation of this trend as anesthesia is deepened would produce a statistically significant incidence of frontal dominance.

It is possible that the supplemental drugs given for clinical anesthesia following the study period in some way influenced the recall of events during the induction of anesthesia. This seems unlikely because all patients received supplemental drugs (although not always the same drug), and because retrograde amnesia is a poorly documented phenomenon that is unlikely to occur for events that take place many minutes before the supplemental drug is given.

In conclusion, the combination of analysis of variance and short-epoch power spectrum analysis provides a statistically valid and powerful technique for determining the significance of changes in the EEG. Using this technique, statistically significant EEG changes have been demonstrated during the transition from the mnemonic to amnesic states with both enflurane and enflurane-nitrous oxide. The nature of these changes is agent-specific, being increased high-frequency activity for enflurane alone, and changes in the frequency and amplitude of the alpha rhythm when enflurane and nitrous oxide are used in combination. Finally, although frontal dominance was observed in a number of cases, it appeared to be a measure of anesthetic depth somewhat deeper than unresponsiveness to verbal command.

References
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