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The Electroencephalogram Does Not Predict Depth of Isoflurane Anesthesia

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Background: **The power spectrum of the electroencephalogram (EEG) may be analyzed to provide quantitative measures of EEG activity (*e.g.*, spectral edge, which defines the highest EEG frequency at which significant activity is found). The current study tested the hypothesis that spectral edge and similar measures distinguish different functional depths of anesthesia in humans.**

Methods: **Three groups were studied. Group 1 consisted of 34 surgical patients (ASA physical status 1 or 2) who received 0.6, 1.0 and 1.4 MAC isoflurane anesthesia. A subgroup (group 2) of group 1 was tested during 1.0 MAC isoflurane anesthesia at surgical incision. Group 3 consisted of 16 volunteers who listened to an audiotape while receiving 0.15, 0.3, and 0.45 MAC isoflurane or 0.3, 0.45, and 0.6 MAC nitrous oxide in oxygen. The audiotape contained information designed to test implicit and explicit memory formation. We tested the ability of six EEG parameters (spectral-edge, 95th percentile power frequency, median power, and zero crossing frequencies and total power in the α- [8–13 Hz] and δ- [<4 Hz] power ranges) to predict movement after surgical incision, purposeful response to command, or memory of information presented during anesthetic administration.**

Results: **Isoflurane decreased EEG activity in group 1 in a dose-related fashion. The 55% of group 2 who made purposeful movements in response to incision did not differ in their EEG from nonresponders (*e.g.*, spectral edge 19.8 ± 3.1 *vs.* 19.3 ± 2.6 Hz, mean ± SD). In group 3, memory of the information presented did not correlate with values of any EEG parameter. Response to verbal command was associated with lower anesthetic concentrations and with smaller α- and δ-band power (298 ± 66 *vs.* 401 ± 80 watts; and 75 ± 20 *vs.* 121 ± 49 watts, mean ± SD), but there was no difference in values for other parameters.**

Conclusions: **We conclude that our EEG measures do not predict depth of anesthesia as defined by the response to surgical incision, the response to verbal command or the development of memory. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: isoflurane. Memory: intraoperative awareness. Monitoring: electroencephalography. Potency: minimum alveolar concentration.)**

ANESTHESIA produces reversible central nervous system (CNS) depression, for which the degree of depression defines the "depth of anesthesia." Cerebral electrical activity varies with anesthetic dose,[1,2] and after computer processing to provide quantitative measures of EEG activity, the electroencephalogram (EEG) may be a useful monitor of anesthetic depth.[3–6] Accordingly, several studies have attempted to correlate depth of anesthesia and various EEG parameters.[3–12] Although some correlations have been found, no parameter has had a sensitivity and specificity sufficient to justify the use of EEG as a reliable monitor of anesthetic depth. Of immediate importance, the EEG does not predict clinical responses to noxious stimuli.[13,14]

Some previous studies may not have adequately tested the usefulness of the EEG because the measures of anesthetic depth (*e.g.*, changes in cardiovascular variables) do not necessarily reflect CNS depression. Other studies may have obscured a relation between depth of anesthesia and EEG by using combinations of anesthetic agents where the individual drugs affect the CNS differently. In the current study we applied a single anesthetic agent to test the ability of currently available, commonly used quantitative EEG parameters to predict depth of anesthesia as defined by response to surgical incision, response to verbal command or memory of verbal information. We also documented the effect of a range of isoflurane and nitrous oxide concentrations on the EEG.

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Materials and Methods

With the approval of the Committee on Human Research of the University of California, San Francisco, we studied 3 groups of patients or volunteers. Group 1 consisted of 34 patients of ASA physical status 1 or 2 scheduled for elective surgery. After induction of anesthesia by inhalation of isoflurane in oxygen and nitrous oxide, supplemented in 18 patients by small doses of propofol (1.2 ± 0.6 mg/kg intravenously, mean ± SD), we gave vecuronium bromide 0.07 mg/kg to facilitate tracheal intubation and mechanically ventilated the lungs to provide normocapnia. Anesthesia was maintained with isoflurane in oxygen. End-tidal concentrations of carbon dioxide and isoflurane were continuously monitored by mass spectrometry. Residual neuromuscular blockade was assessed by "train-of-four" stimulation of the ulnar nerve.

As previously described in detail,[15] these subjects participated in a study to assess learning during anesthesia. The protocol tested both conscious (explicit) and unconscious (implicit) memory by assessing remembrance of answers to five intriguing, obscure general-knowledge questions (*e.g.*, "What is the blood pressure of an octopus?"), and unconscious (implicit) memory by the compliance with a suggestion to touch one's ear during the postoperative interview. Audiotape recordings of the information to be learned were supplied to each subject though a headset. The EEG was recorded at least 15 min after the last administration of propofol or nitrous oxide, and after at least 10 min at a stable end-tidal concentration of 0.6 MAC isoflurane, and before the start of surgery.

In 18 patients (group 2), a subgroup of the above 34 patients, neuromuscular blockade resolved (*i.e.*, response to train-of-four stimulation returned to normal) before skin incision, allowing observation of the motor response to surgical incision. Incision was made in group 2 at least 30 min after induction of anesthesia and after at least 10 min at an end-tidal isoflurane concentration of 1.0 MAC (age-adjusted). The EEG was recorded for 1 min before skin incision. For 1 min after incision, we observed the patients for movement of the limbs or head. The patients received additional vecuronium, 0.1 mg/kg intravenously, and surgery proceeded.

During surgery, the EEG was again recorded in all patients in group 1 (and group 2) after equilibration for at least 10 min at 1.0 and 1.4 MAC isoflurane. Five answers to general-knowledge questions were presented at two of the three concentrations studied (0.6, 1.0 and 1.4 MAC). The subjects were evaluated for memory of the presented material on the 1st postoperative day. We later use these data to assess the effect of anesthetic concentration on the EEG.

Two channels of EEG, F_{p1}-mastoid 1 and F_{p2}-mastoid 2, were recorded. The signal was amplified, prefiltered (0.5–30 Hz), and digitized at 128 Hz (eight-bit resolution) with a Cerebrotrac monitor (SRD, Misgav, Israel). The digitized EEG was transferred in real-time to a Macintosh SE (Apple, Cupertino, CA) computer where, with custom software‖ previously described,[16] the data underwent time-domain analysis, fast Fourier transformation, and power spectral analysis. In patients in group 1, four sequential, artifact-free epochs (total = 16 s per patient) were recorded at stable end-tidal concentrations of 0.6, 1.0, and 1.4 MAC isoflurane. In group 2 (neuromuscular blockade resolved), four epochs (16 s) immediately preceding surgical incision were analyzed. We visually inspected all recording intervals of the preceding 30 s to ensure stability of the EEG signal through the analysis period. Six quantitative EEG parameters were calculated: zero crossing, median power, 95th percentile power, and spectral-edge frequencies; absolute δ-band (<4 Hz) power; and absolute α-band (8–13 Hz) power.

Values for the six EEG parameters were compared between movers and nonmovers in group 2 by using unpaired two-tailed *t* tests. EEG parameters at 0.6, 1.0, and 1.4 MAC isoflurane were compared to test the effect of increasing anesthetic dose on the EEG (analysis of variance and Dunnett's test). EEG parameters were compared between 1.0 MAC isoflurane before surgery and 1.0 MAC isoflurane during surgery (paired *t* test) to test the effect of ongoing stimulation. A P value ≤ 0.05 was considered statistically significant.

We previously assessed memory and responsiveness in 16 male volunteers (18–34 yr) at subanesthetic concentrations of isoflurane or nitrous oxide.[17] We now report the EEG findings in these volunteers (group 3). Subjects were interviewed on the day of the study, asked 20 obscure but interesting general-knowledge questions (*e.g.*, "What is the blood pressure of an octopus?") and were told they would hear the answers to these questions during administration of isoflurane or nitrous oxide. Their recollection of the correct answers was tested subsequently with a five-choice (multiple-choice) test.

‖ The software is available for noncommercial use from Dr. Rampil.

Subjects breathed from a semiclosed anesthetic circuit *via* a mouthpiece. A nose-clip prevented nasal inspiration of room air. Gas was sampled continuously from a port at the mouth-piece for analysis of end-tidal concentrations of isoflurane, N_2O, and carbon dioxide by mass spectrometry. A deadspace of 100 ml, separating the sampling point from the anesthetic circuit, prevented contamination of end-tidal samples with inspired gas. The EEG was recorded as for group 1. Recordings were made with the eyes closed before administration of the anesthetic agent and at each anesthetic dose after 15 min at a stable end-tidal anesthetic concentration.

After each subject breathed oxygen for 3 min, either isoflurane or nitrous oxide (prospectively randomized) was introduced and the inspired concentration adjusted to achieve target end-tidal concentrations. One to 3 weeks after the first study in group 3, the experiment was repeated with the alternate anesthetic agent in the same protocol and 20 new general-knowledge questions (see below). For isoflurane, the end-tidal concentration sequence was 0.15, 0.3, 0.45, and 0.15 times MAC, and for nitrous oxide the sequence was 0.3, 0.45, 0.6, and 0.3 times MAC. Previous data[7,18–21] suggested that these ranges of concentrations of nitrous oxide and isoflurane would permit and prevent purposeful response and memory. MAC for isoflurane was assumed to be 1.28% in this age group,[22] and MAC for nitrous oxide to be 1.04 atm.[23] After maintaining each end-tidal concentration for 15 min to allow equilibration among end-tidal, arterial, and cerebral partial pressures of anesthetic agent, subjects were tested for their ability to respond purposefully to a verbal command by asking them to open their eyes and to squeeze an observer's fingers a stated number of times. At two or three of the three concentrations they received a taped message (*via* a set of headphones) containing the answers to five of the general-knowledge questions (randomly allocated) presented before the study began. Each answer was repeated three times.

On the day after each study, an investigator unaware of which questions had been answered during anesthesia conducted an interview to determine how much of the information presented at different anesthetic concentrations could be recalled. Subjects were presented with the same 20 general-knowledge questions with five multiple choice answers for each question, one correct, the rest incorrect "distractors." After answering the questions, subjects were asked to identify any answers they consciously recalled hearing during the study.

As noted above, at one anesthetic concentration (randomly assigned), no answers were provided. Thus five randomized questions of the total were unanswered, permitting the number of correct answers (*i.e.*, guesses or baseline knowledge) to these five questions to act as controls for each of the seven groups of five questions whose answers were provided during anesthesia. Questions the answers to which were known before the study were excluded from analysis for that subject. Wilcoxon's matched-pair test was used to determine whether learning occurred at each anesthetic concentration by comparing scores (percentage correct) for questions answered at that concentration with scores for control (unanswered) questions.

For group 3 the EEG was analyzed as for groups 1 and 2. Mean values were calculated over 40 s (contiguous and artifact-free) at each concentration of each agent.

Mean values of EEG parameters while awake (eyes closed) were compared with values at 0.15, 0.3, 0.45, and 0.6 MAC (analysis of variance and Dunnett's test). Mean values of EEG parameters were compared between the early and late administrations of isoflurane and the early and late administrations of nitrous oxide (paired t test). The relation between EEG parameters and depth of anesthesia was assessed as follows.

1. EEG parameters at the highest anesthetic concentration allowing purposeful response to verbal command were compared with parameters at the lowest concentration preventing purposeful response in each subject. For example, if a subject responded at 0.3 MAC but not at 0.45 MAC isoflurane, we compared EEG parameters at 0.3 and 0.45 MAC (paired t test).
2. EEG parameters from concentrations of isoflurane that did and did not permit learning were compared (paired t test).
3. The correlation between the EEG at each anesthetic concentration and (1) the number of correct answers to questions and (2) the number of answers consciously recalled was assessed (Spearman's rank-order correlation coefficient).

These analyses were performed separately for each agent (isoflurane and nitrous oxide). A P value of ≤ 0.05 was considered significant.

Results

Demographic data are presented in table 1. Two volunteers (group 3) failed to complete the nitrous oxide study because of severe nausea and vomiting. Therefore data relating to the nitrous oxide part of the study are from 14 subjects.

During isoflurane administration in groups 1 and 3, EEG varied predictably with increasing end-tidal concentration (fig. 1). EEG activity (median power frequency and zero crossing frequency) increased at low concentrations of anesthetic compared with awake values (group 3). EEG activity decreased at anesthetizing isoflurane concentrations (1.0 and 1.4 MAC) compared with values at 0.6 MAC (group 1). EEG parameters did not differ between 1.0 and 1.4 MAC isoflurane. EEG burst suppression was only seen at 1.4 MAC. No EEG parameter differed between the first and second administrations of 0.15 MAC isoflurane or between the first and second administrations of 0.3 MAC nitrous oxide (group 3).

During nitrous oxide administration to volunteers, we found a similar trend of increasing EEG activity (95th percentile power frequency and zero crossing frequency) at subanesthetic concentrations; higher MAC-fractions of this agent were not tested because of potential hypoxia (fig. 2).

As previously reported, no learning occurred in group 1.[15] Thus, we could not test the ability of the EEG to predict learning as we has intended.

In group 2, no EEG parameter before surgical incision differed between patients who subsequently moved and those who did not move in response to incision (table 2). Four of eight patients in this group given propofol at induction (1.2 ± 0.4 mg/kg, mean ± SD) moved at incision, and four did not. No EEG parameters differed at any time between those who had received propofol and those who had not.

In group 3, subanesthetic concentrations of isoflurane and nitrous oxide decreased purposeful response and memory in a dose-related manner.[17] At any given concentration of isoflurane or nitrous oxide, the EEG measures did not correlate with either the presence vs. absence of conscious recall or with numbers of correct answers to questions.

Isoflurane at 0.3 MAC allowed purposeful response in all but one volunteer, whereas 0.45 MAC prevented purposeful response in all but two. Thus, comparisons of EEG at these end-points were comparisons of the effects of anesthetic concentration. During isoflurane administration, spectral-edge, zero crossing, median power, and 95th percentile power frequencies did not differ between concentrations at which subjects were responsive or unresponsive to verbal command (table

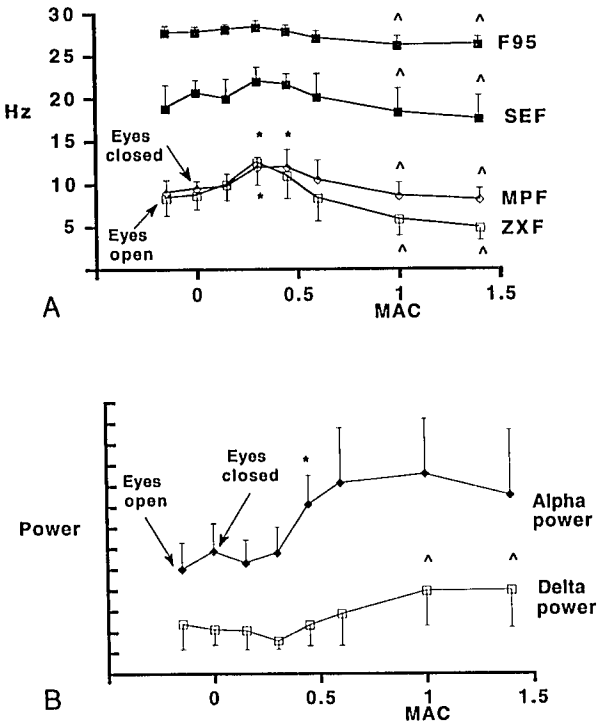

Fig. 1. (*A*) Electroencephalographic parameters during isoflurane administration (groups 1 and 3): spectral-edge (SEF), zero crossing (ZXF), median power (MPF), and 95th percentile power frequencies (F95), expressed in hertz. (*B*) Band power in the δ- and α-frequency ranges is expressed as uncalibrated watts (mean ± SD). These data illustrate a peak acceleration of activity at 0.3 MAC, with slowing at higher concentrations. The slowing at isoflurane concentrations greater than 0.45 MAC shifted power from the β range into the α and δ ranges. Increased synchrony also increased the α and δ power at these concentrations. *$P < 0.05$, difference between EEG parameters awake (eyes closed) and during administration of isoflurane; ∧$P < 0.05$, difference between EEG parameters at 0.6 MAC and at greater concentrations of isoflurane.

Table 1. Demographic Data for the Patients and Volunteers Studied

Group	1	2	3
n	34	18	16
Age (yr)	38 ± 10	40 ± 10	25 ± 4
Weight (kg)	74 ± 14	77 ± 16	77 ± 9
Male/female (n)	15/19	10/8	16/0

Data are mean ± SD.

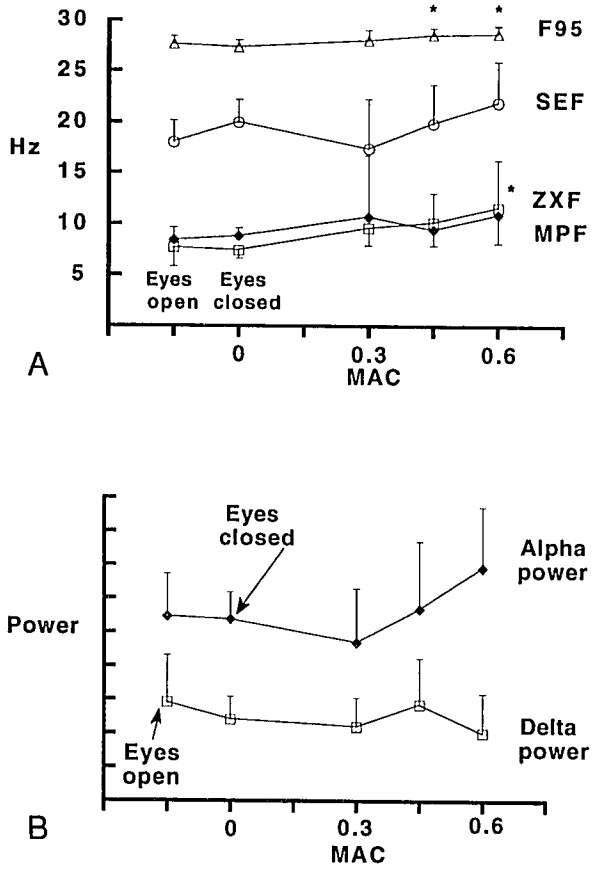

Fig. 2. (*A*) Electroencephalographic parameters during nitrous oxide administration (group 3): spectral-edge (SEF), zero crossing (ZXF), median power (MPF), and 95th percentile power frequencies (F95), expressed in hertz. (*B*) Band power in the δ- and α-frequency ranges is expressed as uncalibrated watts (mean ± SD). F95 and ZXF increased with nitrous oxide administration relative to the awake state. *$P < 0.05$, difference between EEG parameters awake (eyes closed) and during administration of nitrous oxide.

2). Values for α power and δ power were significantly greater at concentrations producing unresponsiveness. These observations also apply to the concentrations affecting learning because they were identical to those that affected responsiveness (fig. 1). Finally, learning occurred at all concentrations of nitrous oxide studied,[17] thus no comparisons could be made between concentrations permitting and preventing learning.

Ten out of 14 subjects continued to respond at the highest concentrations of nitrous oxide studied (0.6 MAC), and EEG data were available for only 3 of the remaining 4 nonresponders. Although the numbers were too small to make valid statistical comparisons, the data did not suggest a trend to differences in EEG parameters in responders and nonresponders.

EEG parameters at 1.0 MAC isoflurane before surgery (group 2, table 2) did not differ from the same parameters at 1.0 MAC isoflurane during surgery (group 1, fig. 1). That is, we found no effect of ongoing surgery on the EEG.

Discussion

EEG activity varies with increasing anesthetic dose, a finding consistent with the classic descriptions by Martin *et al.*[2-4] Our data confirm initial desynchronization and acceleration of the EEG at low concentrations of isoflurane or nitrous oxide, and slowing and increased amplitude of the EEG with further increases in concentration.

In conflict with our hypothesis, we failed to demonstrate that the EEG might distinguish between different clinical measures of depth. The EEG did not predict movers *versus* nonmovers at 1.0 MAC, and the EEG did not predict recall of verbal information presented during anesthesia. Although δ power and α power were significantly greater at the higher isoflurane concentrations preventing purposeful response to verbal command and preventing learning, in any individual, numbers of correct answers did not correlate with δ power or α power at either concentration. It therefore seems likely that this is a dose-related phenomenon rather than a specific index of depth of anesthesia. Nevertheless, changes in δ and α power may be a warning of light anesthesia, and in a previous study, increased δ power predicted imminent eye-opening.[7] No other EEG parameters differed significantly between different states of responsiveness. These findings are consistent with previous findings of a lack of specificity and sensitivity of the EEG in predicting depth of anesthesia.[7,11,25]

The use of nitrous oxide and propofol to facilitate induction with isoflurane could have influenced the values for EEG parameters in groups 1 and 2. However, at least 15 min elapsed between discontinuing administration of both agents and EEG recording at 0.6 MAC. By this time the end-tidal concentration of nitrous oxide was less than 5% in all patients and usually much lower, with an end-tidal nitrous oxide concentration of 2.4 ± 0.6%. This concentration of nitrous oxide is unlikely to influence the EEG.# No EEG parameter differed be-

Rampil IJ: Unpublished data.

Table 2. Electroencephalographic Parameters in Patients Who Did and Did Not Move in Response to Surgical Incision at 1.0 MAC Isoflurance (Group 1) and in Volunteers Who Did and Did Not Respond to Verbal Command (Group 3)

	Group 1		Group 3	
	Move	No Move	Response	No Response
n	10	8	16	16
F95	26.5 ± 0.7	27.1 ± 0.8	28.4 ± 0.7	27.7 ± 0.8
SEF	19.8 ± 3.1	19.3 ± 2.6	22.1 ± 1.7	21.3 ± 1.3
MPF	9.1 ± 0.7	9.5 ± 1.3	12.3 ± 1.4	11.6 ± 2.1
ZXF	6.3 ± 0.9	6.7 ± 1.6	12.6 ± 2.5	10.5 ± 2.3
α power	494 ± 102	471 ± 99	298 ± 66	401 ± 80*
δ power	166 ± 42	160 ± 52	75 ± 20	121 ± 49*

Ninety-five-percent spectral edge frequency (F95), median power frequency (MPF), spectral edge frequency (SEF) and zero crossing frequency (ZXF) are expressed as hertz; band power in the δ and α frequency ranges is expressed as uncalibrated watts (mean ± SD).

* $P < 0.05$ (between Response and No Response)

tween those who received propofol and those who did not, also suggesting that the previous administration of propofol and nitrous oxide had little influence on the EEG.

At least 30 min elapsed between discontinuation of propofol and nitrous oxide administration and incision. The previous administration of propofol did not alter the incidence of movement in response to incision or EEG parameters at 1.0 MAC isoflurane. We did not demonstrate any difference between EEG parameters at 1.0 MAC before *versus* after incision or during surgery. This differs from the results of Kochs *et al.*,[26] who examined a 17-electrode topographic mapping of spectral features and found that surgical incision produced focal EEG slowing, most prominently in the frontal leads. The frontomastoid leads used in the current study would not be very sensitive to small degrees of focal slowing.

In the volunteer group, we provided a sequence of anesthetic administration in which the first (and lowest) dose was repeated after several hours of exposure to higher doses. There was no apparent difference in EEG between the initial and late exposures to 0.15 MAC isoflurane or 0.3 MAC nitrous oxide. Acute tolerance to nitrous oxide has been reported,[27] but in that study, the δ waves (0–3 Hz) that accompanied the administration of nitrous oxide (superimposed on steady-state halothane) accelerated to the θ range (4–7 Hz) within 13 min. We did not begin recording and analyzing the EEG until the anesthetic had been steady for at least 15 min. Under these conditions, we saw no evidence to support tolerance to either nitrous oxide or isoflurane.

Recent work shows that even near-complete depression of cortical electrical activity by isoflurane or thiopental (burst suppression) in rats[13] and in humans[14] does not guarantee lack of movement in response to noxious stimulus. This suggests that such a response may be controlled by or transferred to subcortical centers during anesthesia. Our observation in rats that acute decerebration (removal of the part of the CNS—cortex and thalamus—responsible for EEG generation) does not affect the concentration of isoflurane required to suppress movement in response to tail-clamping supports this hypothesis.[28] Other evidence also suggests that the motor response may be primarily mediated by the spinal cord, at least in lower animals.[29,30] The data presented in the current report support the observation that, with currently available technology, the EEG is not a reliable or useful guide to the clinical adequacy of anesthesia in preventing movement, response to verbal command and, perhaps most importantly for the clinician, learning during anesthesia and conscious recall of events during anesthesia. Although there is a dose–response curve relating "depth" and EEG, the slope of the curve appears to be shallow, leading to a wide range of EEG where the likelihood of response is of intermediate probability and thus not very useful. The dose–response curve relating isoflurane concentration to likelihood of movement during pure isoflurane–oxygen anesthesia serves as a contrast: a steep slope at 1.0 MAC separates responders from nonresponders. The only exception to this gloomy assessment is that δ power or α power may be useful in predicting whether subjects retain the ability to respond purposefully to verbal command or to retain verbal infor-

mation in memory, but this utility is no greater than that provided by measuring the end-tidal concentration of anesthetic.

Other methods of analysis of cerebral electrical activity may prove to be better assessors of depth of anesthesia. We confined ourselves to signal processing and analysis techniques similar to those used in commercially available EEG monitors. We conclude that although there was a dose–response to inhaled anesthetics, the EEG as quantified by nonparametric time-domain or frequency-domain techniques is not a reliable guide to depth of anesthesia.

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