# The Electroencephalographic Effects of Desflurane in Humans

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The electroencephalographic (EEG) effects of a new inhaled anesthetic are of interest because of the potential of such agents to produce excitatory (convulsant) activity and because of the potential usefulness of the EEG as an indicator of anesthetic depth and cerebral activity. Accordingly, we examined the EEG in 12 healthy, young male volunteers during desflurane anesthesia. Each subject had a baseline recording and then steady-state exposure to 6, 9, and 12% (0.83, 1.24, and 1.66 MAC) desflurane in $O_2$ alone, and to 3, 6, and 9% desflurane in $O_2$ with 60% $N_2O$. The sequence of doses and the presence of $N_2O$ were randomized. We used mechanical ventilation to maintain normocapnia at each dose level. We also tested the effects of hypercapnia secondary to spontaneous ventilation. Additionally, at 1.24 MAC, subjects' lungs were hyperventilated to a $P_{CO_2}$ of 25.8 ± 0.7 mmHg and exposed to rhythmic, loud clapping to attempt to provoke excitatory phenomena. Finally, after at least 6 h exposure to desflurane, we repeated measurements at 0.83 and 1.66 MAC to assess possible tolerance. Four channels of EEG were monitored visually, and at each dose, a quantitative EEG analysis was performed. Desflurane produced EEG changes comparable to those observed with equipotent levels of isoflurane. No epileptiform activity was seen. Desflurane significantly suppressed EEG activity; prominent burst suppression was seen at 1.24 MAC and higher. Substitution of $N_2O$ for 0.42 MAC desflurane reduced the degree of EEG suppression relative to the equipotent administration of desflurane and $O_2$. Quantitative EEG measures for the early doses and for the later, repeated exposures did not differ. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: desflurane (I-653). Brain: electroencephalogram.)

DESFLURANE, A DERIVATIVE of isoflurane, has lower solubility than isoflurane and therefore more rapid pharmacokinetics.[1] Halogenated ethers, a class of potent anesthetics to which these drugs belong, have a wide range of effects on electroencephalographic (EEG) activity and brain metabolism. Isoflurane, for example, causes profound EEG depression,[2] whereas enflurane at higher concentrations may cause epileptiform activity, particularly

in the presence of hypocapnia.[3] Flurothyl (Indoklon) is a potent epileptogen.[4] Clinical evaluation of desflurane, as a halogenated ether, should determine whether it causes a depression of brain electrical activity or, conversely, a potentially detrimental excitement.

Previous studies in juvenile swine indicate that desflurane produces dose-related depression of EEG activity, up to and including burst suppression. In this animal, increasing doses of desflurane produced EEG depression statistically indistinguishable from that produced by isoflurane in approximately equipotent concentrations.[5] The current report extends these studies to humans. We report the EEG response of normal, young volunteers to graded concentrations of desflurane with or without $N_2O$, at high, low, and normal levels of arterial $CO_2$ tension ($Pa_{CO_2}$).

## Materials and Methods

The study protocol was approved by the Human Experimentation Committee of the University of California, San Francisco. We enrolled 12 healthy, young male volunteers aged 23.8 ± 2.6 yr (mean ± SD) after obtaining informed, written consent. Selection criteria used to determine eligibility included: absence of neuropsychiatric disease and complete abstinence from recreational drug use, including alcohol. Subjects fasted for at least 8 h and refrained from any drugs that might have central nervous system effects, including caffeine and tobacco, for at least 12 h before the study. No preanesthetic medication was given.

On the morning of study, subjects reclined supine, and pressure points were carefully padded. A left radial arterial catheter was inserted to monitor arterial pressure and to obtain samples for blood gas analysis. Eight 30-G, subdermal needle electrodes (model E-2, Grass Instruments, Quincy, MA) were placed in the following International 10–20 System locations: FP1, FP2, C3, C4, P3, P4, O1, and O2 to create a bilateral, bipolar frontocentral, and parietooccipital montage. The electrodes were adjusted, if necessary, to balance all contact impedances between 5–10 kΩ. The needle electrodes were well tolerated by all subjects. After electrode placement, subjects rested with room lights dimmed and eyes closed for at least 20 min before we recorded a baseline EEG.

The anesthetic study design was a semirandomized exposure to desflurane 6, 9, and 12% (0.83, 1.24, 1.66 MAC respectively) and, in some subjects, 15% (2.08 MAC). The two lowest concentrations were administered first, in random order, followed by 1.66 MAC. We choose this sequence because the hemodynamic effects of moderate-

to-high doses of desflurane were not known at the outset of the study, and there was concern that the 1.66 MAC dose induced excessive hypotension. Subjects who tolerated 1.66 MAC well also received 2.08 MAC.

$N_2O$ was administered to all subjects in a crossover design in which 60% $N_2O$ was substituted for 3% (0.42 MAC) desflurane. The concentration sequence was repeated for both desflurane in $O_2$ and desflurane and $N_2O$ in $O_2$. The use of $N_2O$ for induction and first sequence was randomized and resulted in six subjects' receiving the $N_2O$ combination first.

Anesthesia was induced by inhalation of desflurane with or without $N_2O$ *via* mask. The trachea was intubated without the use of adjuvant drugs. Mechanical ventilation was adjusted to produce a $Pa_{CO_2}$ of 30–35 mmHg, and normothermia was maintained with a Bair Hugger® forced-air warmer (model 200, Augustine Medical, Eden Prairie, MN).

Anesthesia was induced with desflurane in $N_2O$ and $O_2$ in six subjects and desflurane in $O_2$ in six. Four subjects received 2.08 MAC desflurane in $O_2$, and six subjects received 2.08 MAC with $N_2O$.

For each MAC level, we attained the desired end-tidal concentration and then continued equilibration for at least 12 min before we measured EEG activity. After obtaining EEG measurements, we obtained an arterial blood sample to verify that the $Pa_{CO_2}$ equalled 35–40 mmHg. Spontaneous ventilation then was instituted. After a 12-min period allowed for each subject to reach a steady-state ventilatory pattern, we repeated the EEG and arterial blood gas measurements. This process was repeated with spontaneous ventilation at the three (or four, if tolerated hemodynamically) MAC levels.

After the sequence of concentrations at normocapnic and hypercapnic states, mechanical ventilation was adjusted to create a $Pa_{CO_2}$ of ≈25 mmHg at 1.24 MAC. During this hypocapnic test, the subject was stimulated by repetitive, 1-Hz hand clapping lasting 60 s at the subject's head in an effort to evoke epileptiform activity. Finally, after at least 6 h of anesthesia, the 0.83 and 1.66 MAC doses with normocapnia were repeated with the initial background gas, either $O_2$ or $N_2O/O_2$, to assess any possible long-term tolerance or other instability of response related to duration of anesthesia.

EEG signals from the four-channel montage were amplified, filtered, and displayed by a Brain-Mate® system (Interspec, Ambler, PA). Input amplifiers were set to pass signals in the range of 1.0–30 Hz, and gain was set to provide a full-scale reading for 160 $\mu V$ peak-to-peak. The digitized, raw EEG waveforms were displayed continuously in real time on a Macintosh SE (Apple Computer, Cupertino, CA) at the standard sweep speed of 30 mm/s throughout the protocol. These waveforms were monitored for evidence of epileptiform or other atypical ac-

tivity. Two to 5 min of noise-free raw signals were recorded for off-line quantitative analysis on an analog tape recorder (model C-4, AR Vetter, Rebersburg, PA) after the period of steady-state equilibration at each dose.

Quantitative EEG (QEEG) analysis was performed with a Macintosh IIx and a "virtual" analyzer created with LabView® software (National Instruments, Austin, TX). The off-line analyzer sampled all channels at 128 Hz with 12-bit resolution and calculated the following parameters[6]: zero crossing frequency (ZXF), median power frequency (MPF), spectral edge frequency (SEF),[7,8] and burst suppression ratio (BSR).[5] To improve noise immunity, the BSR algorithm was modified slightly to recognize suppression intervals longer than 0.5 s, rather than the original 0.24 s. To adjust the SEF empirically to reflect the presence of periods of suppression, an additional parameter, the burst-compensated SEF (BSEF), was calculated:

$$BSEF = SEF\left(1 - \frac{BSR}{100}\right)$$

Parameters were calculated for 4-s epochs and reported as means over the entire recording interval. Longer recording intervals were chosen to compensate for doses that produced nonstationary** EEG activity, such as burst suppression.

This protocol also provided an opportunity to assess the relative efficacy of the calculated QEEG parameters as monitors of anesthetic "depth"—specifically, the ability to discriminate among different concentrations of desflurane anesthesia. We assessed this with a figure of merit (FOM), which indicated the magnitude of the change in the parameter over the 0.83–1.66 MAC range as a fraction of the full scale of the parameter. The full-scale range for the BSR was 100 (%) and 30 (Hz) for the other parameters.

QEEG data were compared by analysis of variance with repeated measures or two tailed $t$ tests, as appropriate. Differences were considered significant when $P < 0.05$.

## Results

In the awake volunteer, the EEG dominant frequency from the anterior scalp was significantly faster than that from the posterior scalp. This finding was most prominent in the MPF and less so in the ZXF and SEF (fig. 1). Induction of anesthesia eliminated any differences between QEEG parameters calculated from the frontocentral and parietooccipital leads. There were no interhemispheric

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** "Nonstationary" refers to statistical instability; *i.e.*, the quantitative EEG parameters computed during burst suppression, a nonstationary activity, vary widely from second to second. Nonstationary conditions violate many of the assumptions involved in digital signal processing.
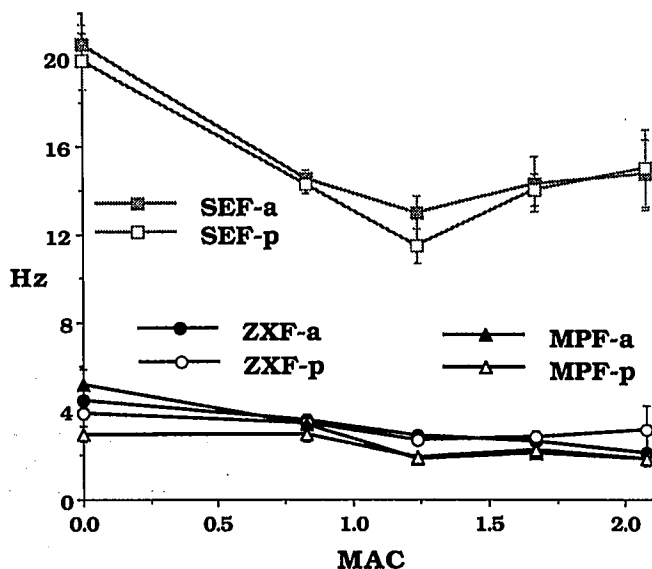
FIG. 1. Comparison of anterior *vesus* posterior frequency distribution during desflurane anesthesia, (FP1-C3 (a) and P3-O1 (p)). In awake subjects, there was a tendency toward higher frequencies in the anterior lead that became significant in the MPF parameter. This spatial inequality disappeared during administration of desflurane.

(right *vs.* left) differences. Therefore, QEEG results reported here are from FP1-C3 unless otherwise noted.

Desflurane caused a depression of cortical electrical activity (fig. 2). No epileptiform or other aberrant activity was seen at any time. With increasing anesthetic doses, background activity initially slowed and then increasingly was suppressed without further slowing. Thus, frequency-based QEEG measures (ZXF, MPF, and SEF) detected progressive slowing in the change from awake to 0.83 MAC, and further slowing at 1.24 MAC. Once burst suppression had begun (at 1.24 MAC in most subjects), the frequency content of the remaining bursts of activity

did not slow further with increasing concentrations of desflurane (fig. 3), but did increase the degree of cortical suppression as characterized by the BSR and BSEF. The EEG signals were quantitatively stable less than 5 min after a change to a new end-tidal concentration.

The substitution of 60% $N_2O$ for 3% desflurane (approximately 0.45 MAC in this age group[9]) was associated with significantly increased EEG activity (decreased burst suppression when suppression was present and increased frequency content at lower concentrations) at all same-dose (MAC) levels except 1.24 MAC.

At 1.24 MAC, changes in ventilation altered the $P_{CO_2}$ from 25.7 ± 0.83 mmHg during hyperventilation to 57.53 ± 1.75 mmHg (table 1) during spontaneous ventilation. These alterations in $P_{CO_2}$ did not alter either the frequency content (fig. 4A) or the degree of burst suppression (percentage of time the EEG showed near-isoelectricity) (fig. 4B) at 1.24 MAC.

Repetitive auditory stimuli (hand clapping) during hyperventilation at 1.24 MAC, with and without $N_2O$, caused clearly visible middle- and long-latency evoked potentials (up to 1,000 ms), particularly when suppression of background activity was otherwise present.

The EEG at 0.83 and 1.66 MAC after an additional 6 h of exposure to desflurane demonstrated that the burst suppression phenomena was nonstationary, having a frequent tendency to appear and fade at inconstant intervals. On average, the degree of burst suppression at 1.66 MAC at the end of the study did not differ from that at the beginning (fig. 5). During desflurane in $O_2$ the first trial yielded a mean BSR of 40.4 ± 18% and the second trial a BSR of 34.9 ± 13% (P = 0.81). In the presence of $N_2O$, the mean BSR was initially 2.9 ± 1.3%, and during the repeated trial the BSR was 0.4 ± 0.25% (P = 0.85).

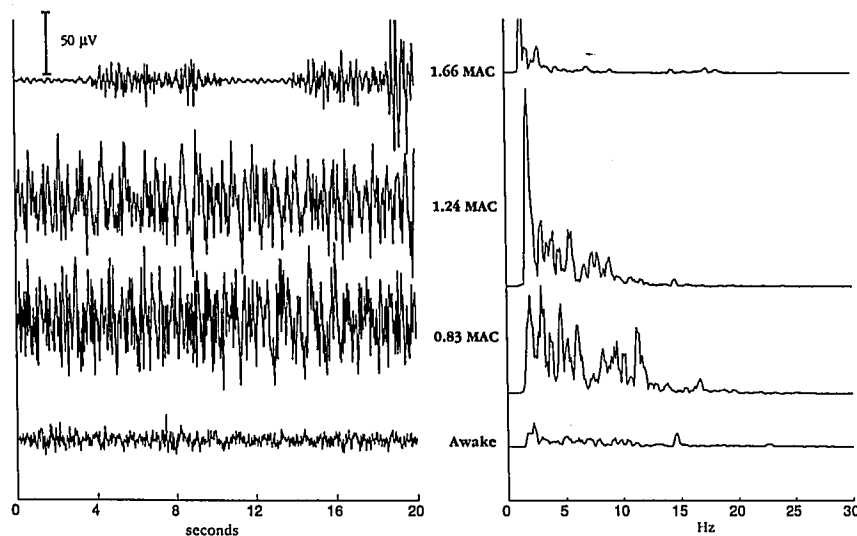The QEEG parameters correlated to some extent with



FIG. 2. Representative EEG waveform data from a single subject. For each dose level, 20 s of data. The awake EEG contains low-amplitude, high-frequency (beta) activity typical of the eyes-open state. The corresponding spectra shows low-amplitude but wide-band activity, extending up to an SEF of 23 Hz. The 0.83 MAC level contains predominantly alpha, theta, and delta activity and a lesser contribution of beta activity. The mix of frequencies in the 1.24 MAC reveals a shift to predominantly theta and delta activity. The 1.66 MAC trace demonstrates burst suppression (BSR = 40%), and the high-frequency character of the burst activity (SEF = 18 Hz). All tracings were obtained during normocapneic mechanical ventilation, except for the awake state, which was obtained during normocapneic spontaneous ventilation.
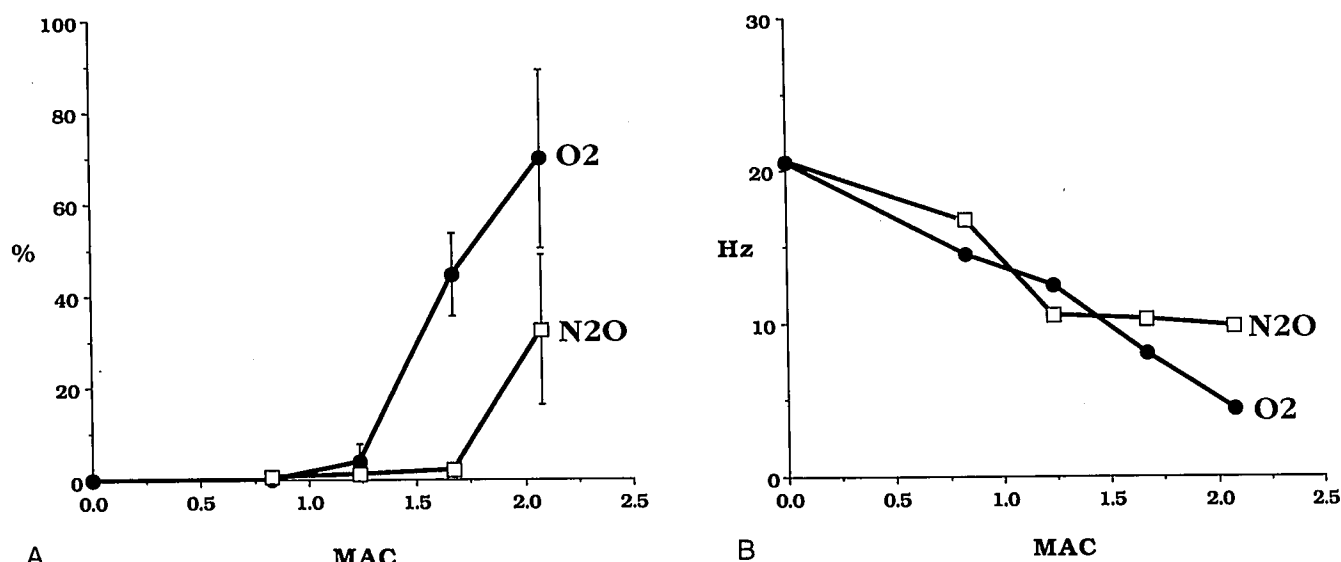
FIG. 3. EEG dose–response curves for two different QEEG parameters reveals differing degrees of change elicited by desflurane. (A) BSR; (B) burst-compensated SEF. Solid symbols denote desflurane in $O_2$ only; open symbols denote combination with $N_2O$.

changes in desflurane dose (table 2). Some parameters had a larger signal change and FOM over a clinically useful range of anesthetic concentrations than did others (table 3). During desflurane in $O_2$, the BSR parameter had the largest FOM, indicating that the BSR provided the best discrimination between 0.83 and 1.66 MAC. The standard (uncompensated) SEF had a poor correlation with desflurane concentration; the EEG retained high-frequency activity during the intermittent bursts that occurred at the higher doses. The BSEF performed better than did the other frequency-based parameters, which did not account for the presence of burst suppression in their algorithms. During desflurane with $N_2O$, there was slowing with little burst suppression in the 0.83–1.66 MAC range, and therefore, the frequency-based parameters all performed with higher FOM than did the BSR.

## Discussion

With increasing concentration, desflurane produces a pattern of increasing cortical depression. Desflurane and isoflurane appear to induce similar levels of cortical depression at similar MAC multiples in humans. Eger et

al.[2] found (with a manual-measurement algorithm) electrical silence 5% of the time at 0.96 MAC isoflurane and 31% of the time at 1.46 MAC, and found complete silence at 1.96 MAC; these results suggest a curve slightly to the left of that in figure 3A. Both agents appear to preserve high-frequency EEG activity within the intermittent bursts.[2] Moderate concentrations of enflurane, given under conditions of hypocapnea, in the presence of auditory stimulation predispose to epileptiform activity in dogs,[10] swine,[5] and humans.[3] Like isoflurane, desflurane does not generate epileptiform activity, even with the addition of hypocapnia and auditory stimulation.

Other potent anesthetics that depress the EEG also depress the cerebral metabolic rate ($CMR_{O_2}$), suggesting that desflurane may also produce a dose-related depression of $CMR_{O_2}$. Lutz et al.[11] report a decline in $CMR_{O_2}$ in dogs (from 3.4 ml · min$^{-1}$ · 100 g$^{-1}$ at 0.5 MAC desflurane to 2.5 ml · min$^{-1}$ · 100 g$^{-1}$ at 2.0 MAC) that was similar to results obtained in dogs with isoflurane.

The substitution of $N_2O$ for 0.45 MAC desflurane increased EEG activity (and diminished BSR) at every dose level above 0.83 MAC. The amount of desflurane sub-

TABLE 1. Blood Gas Values during Different Modes of Ventilation at 1.24 MAC

| Diluent | Ventilation | pH | $P_{CO_2}$ | $P_{O_2}$ |
|---|---|---|---|---|
| $O_2$ | Hyperventilation | 7.57 ± 0.02 | 25.7 ± 0.83 | 492.46 ± 37.56 |
| | Mechnical | 7.44 ± 0.02 | 37.57 ± 1.13 | 463.58 ± 14.60 |
| | Spontaneous | 7.28 ± 0.02 | 57.53 ± 1.75 | 457.67 ± 15.5 |
| $N_2O$ | Hyperventilation | 7.54 ± 0.01 | 25.83 ± 0.68 | 180.68 ± 15.81 |
| | Mechanical | 7.40 ± 0.01 | 39.47 ± 1.63 | 157.27 ± 8.38 |
| | Spontaneous | 7.32 ± 0.01 | 49.63 ± 2.12 | 152.30 ± 10.49 |

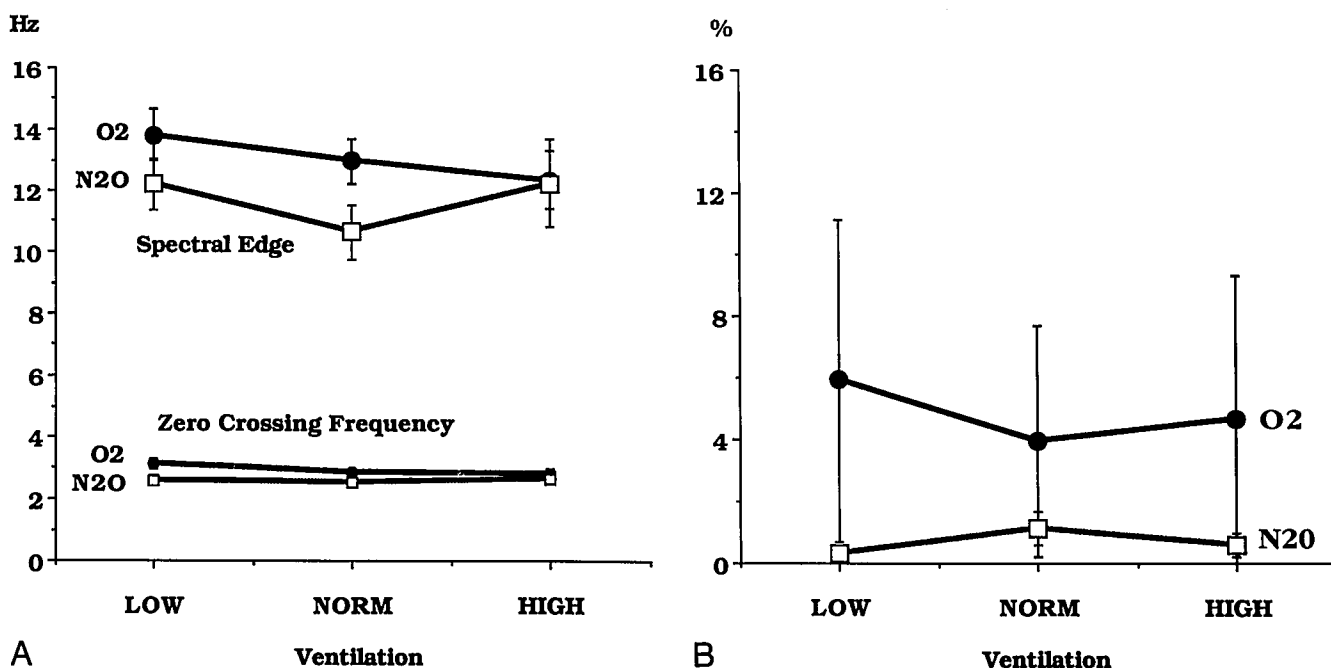All values are expressed as the mean ± SE.

FIG. 4. At 1.24 MAC desflurane there was no difference in either (A) frequency content (as quantitated by SEF and ZXF or (B) degree of suppression (as quantitated by BSR) due to changes in $Pa_{CO_2}$ ranging from 26 (LOW) to 58 (HIGH) mmHg.
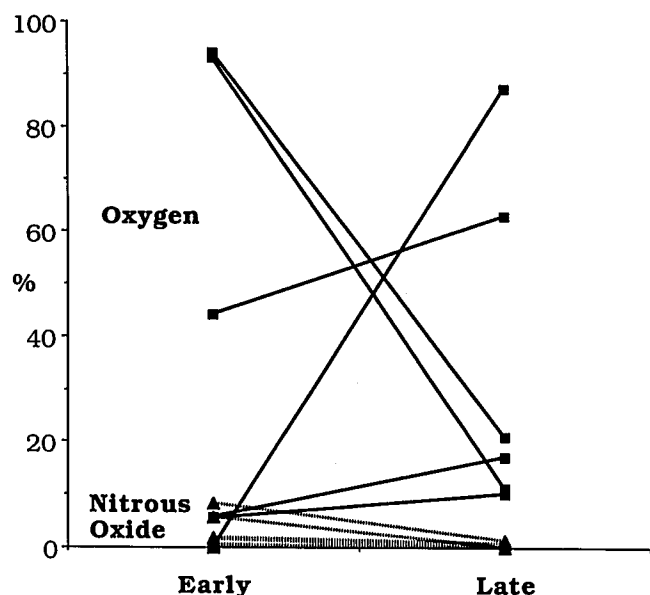


FIG. 5. All of the individual BSR responses of the subjects and their variations over time. Each of the 12 subjects had a set (0.83 and 1.66 MAC) of repeated measurements at least 6 h after the first measurement. The repeated measurements were done either with or without N₂O, depending on whether the individual was randomized to O₂ or N₂O in the first set of measurements. The data plotted represents the BSR at the 1.66 MAC level during normocapnea. The squares are O₂/desflurane subjects; the triangles represent those receiving N₂O as well. There was wide variance due to the nonstationary nature of burst suppression with desflurane, but there was no trend to suggest that BSR was different after a 6-h exposure to desflurane.

stituted for N₂O corresponded roughly to the size of the MAC steps, and the degree of burst suppression with desflurane and N₂O was statistically indistinguishable from that with desflurane alone at the next lower MAC step. Therefore, this effect may be due to the substitution of a relatively "inert" compound (from the standpoint of EEG effects). Another possible explanation is that N₂O may have a direct stimulatory action during otherwise steady-state anesthesia with volatile anesthetics.††

The current study detected no evidence of acute tolerance to desflurane in the human EEG. This finding agrees with prior observations in swine,[5] but is at variance with the suggestion of Lutz *et al.*[11] in dogs. There are several possible explanations of this variance. First, burst suppression is highly nonstationary, and a given subject will have a variable degree of EEG suppression at a given point in time, such that the utility of the measurement may be diminished. Second, there are interspecies differences. For example, beagle dogs anesthetized with enflurane appear to have a much higher incidence of epileptiform activity than do humans at equipotent concentrations.‡‡ Finally, and perhaps most significantly, the sample EEG waveform presented by Lutz *et al.*[11] as rep-

†† Smith NT, Hoff BH, Rampil IJ, Sasse FJ, Flemming DC: Does thiopental or N2O disrupt the EEG during enflurane? (abstract) ANESTHESIOLOGY 51:S4, 1979

‡‡ Rampil IJ: Unpublished data, 1978.

TABLE 2. Quantitative EEG Parameters: Response to Varying Concentrations of Desflurane

| Carrier | Dose | ZXF | BSR | MPF | SEF | BSEF |
|---------|------|-----|-----|-----|-----|------|
| $O_2$ | 0 | $4.5 \pm 0.2$ | $0.0 \pm 0.0$ | $5.1 \pm 0.7$ | $20.6 \pm 0.9$ | $20.6 \pm 0.9$ |
| | 0.83 | $3.6 \pm 0.1$ | $0.1 \pm 0.1$ | $3.4 \pm 0.4$ | $14.4 \pm 0.4$ | $14.4 \pm 0.4$ |
| | 1.24 | $2.8 \pm 0.1$ | $4.0 \pm 3.7$ | $1.8 \pm 0.1$ | $13.0 \pm 0.7$ | $12.4 \pm 0.8$ |
| | 1.66 | $2.5 \pm 0.1$ | $42.6 \pm 8.7$ | $2.1 \pm 0.2$ | $14.1 \pm 1.2$ | $7.6 \pm 1.0$ |
| | 2.0 | $2.0 \pm 0.2$ | $69.7 \pm 19.4$ | $1.8 \pm 0.2$ | $14.7 \pm 1.6$ | $4.3 \pm 2.7$ |
| | $r^2$ | 0.67 | 0.35 | 0.36 | 0.25 | 0.69 |
| $N_2O$ | 0.83 | $4.2 \pm 0.3$ | $0.5 \pm 0.2$ | $4.2 \pm 0.6$ | $17.1 \pm 0.7$ | $17.0 \pm 0.7$ |
| | 1.24 | $2.5 \pm 0.2$ | $1.1 \pm 0.5$ | $1.8 \pm 0.2$ | $10.6 \pm 0.9$ | $10.5 \pm 0.9$ |
| | 1.66 | $2.4 \pm 0.2$ | $1.5 \pm 0.5$ | $1.4 \pm 0.6$ | $10.4 \pm 0.8$ | $10.2 \pm 0.8$ |
| | 2.0 | $2.8 \pm 0.6$ | $32.4 \pm 16.4$ | $2.6 \pm 0.3$ | $14.5 \pm 1.8$ | $8.4 \pm 1.7$ |
| | $r^2$ | 0.29 | 0.16 | 0.20 | 0.18 | 0.45 |

All data are expressed as the mean ± SE.
The $r^2$ values under each column refer to the correlation coefficient for a linear regression of the corresponding parameter *versus* desflurane concentration. In all cases, the $P$ value (ANOVA) was <0.003.

resentative of suppressed EEG activity prior to tolerance seems not to represent usual burst suppression phenomena, but rather to closely resemble the epileptiform (spike and wave) activity in dogs during enflurane. Perhaps the "tolerance" phenomenon represents a reversion to normal background activity in a species with a high susceptibility to drug-induced epileptiform activity.

The calculation of FOM for the QEEG parameters supports the observation that no single QEEG parameter can adequately describe all the patterns of EEG which might occur during an anesthetic. In this case, during $N_2O$ or low concentrations of desflurane, the parameters that described one part of the frequency spectrum performed best, whereas during higher-dose desflurane in $O_2$, the presence of burst suppression phenomena required a specialized (but easy to implement) calculation to reflect the EEG activity accurately.

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TABLE 3. Figure of Merit for EEG Parameters over a Clinically Useful Range of Anesthetic Concentrations

| QEEG | FOM | |
|------|-----|---|
| | $O_2$ | $N_2O$ |
| BSR | $42.5 \pm 8.6$ | $1.56 \pm 0.5$ |
| SEF | $13.0 \pm 2.5$ | $22.9 \pm 3.5$ |
| ZXF | $3.7 \pm 0.5$ | $6.5 \pm 0.8$ |
| MPF | $5.9 \pm 1.4$ | $9.6 \pm 1.9$ |
| BSEF | $22.9 \pm 3.6$ | $22.8 \pm 3.5$ |

All data are expressed as the mean ± SE.
The figure of merit (FOM) was calculated as:

$$FOM = 100 \left( \frac{|QEEG_{0.83} - QEEG_{1.66}|}{full\ scale} \right)$$

Full scale was 100 for BSR and 30 for all others. The larger the FOM, the larger the relative change in the parameter over the concentration range. Comparison by ANOVA of the FOM for the five QEEG parameters during either $O_2$ or $N_2O$ reveals significant differences in performance of these parameters ($P < 0.0001$).