

Effect of Isoflurane on the Auditory Steady-state Response and on Consciousness in Human Volunteers

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Background: The auditory steady state response (ASSR) is a sustained electrical response of the brain to auditory stimuli delivered at fast rates (30–50 responses/s). The aim of this study was to evaluate the effect of 0.26–0.50% isoflurane on the ASSR and on consciousness, defined as responsiveness to verbal commands.

Methods: Ten volunteers (21–31 yr) participated. Isoflurane was administered at three stable, end-tidal concentrations: 0.26%, 0.38%, and 0.50%. The ASSR in response to 18,000 stimuli (500-Hz tonebursts, 10 ms, 82-dB, the right ear, 35–45 bursts/s) was recorded from the vertex with reference to the right mastoid. Recordings were made during baseline, at each isoflurane concentration, and during recovery.

Results: The mean (SD) ASSR amplitudes were 0.32 (0.23) μ V during baseline, 0.24 (0.17) μ V during 0.26% isoflurane, 0.09 (0.05) μ V during 0.38% isoflurane, 0.04 (0.03) μ V during 0.50% isoflurane, and 0.29 (0.33) μ V during recovery. The amplitude

during baseline and recovery was larger than during 0.38% and 0.50% isoflurane ($P < 0.001$). The amplitude at 0.26% was larger than at the other concentrations ($P < 0.025$). The logarithm of the ASSR amplitude was related linearly to the concentration of isoflurane ($r = 0.85$; $P < 0.0001$). The prediction probability (P_k) for loss of consciousness was 0.95 for both ASSR and measured isoflurane concentration. An ASSR amplitude < 0.07 μ V was always associated with unconsciousness.

Conclusions: The ASSR is attenuated in a concentration-dependent manner by isoflurane. Suppression of consciousness and maximal attenuation of ASSR occur in the same isoflurane concentration range. Profound attenuation of ASSR appears to reflect unconsciousness, defined as unresponsiveness to verbal commands. (Key words: Auditory evoked potentials; brain; 40 Hz rhythms; general anesthetics.)

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THE auditory steady state response (ASSR) is a sustained electrical response of the brain to auditory stimuli delivered at fast rates (20–50 stimuli/s). The response is largest for stimulus rates near 40 responses/s, hence the label "40-Hz ASSR."^{1,2} The ASSR provides a sensitive measure of anesthetic effect. It is attenuated profoundly or abolished during surgical anesthesia with isoflurane in oxygen or oxygen-nitrous oxide or with enflurane in oxygen-nitrous oxide.^{3,4} The ASSR remains attenuated profoundly when the concentration of isoflurane is reduced to a level just sufficient to maintain unconsciousness, defined as unresponsiveness to verbal commands (0.50% end-tidal in oxygen).³ During emergence from isoflurane or enflurane anesthesia, the ASSR remains profoundly attenuated until the return of consciousness, which coincides with a sudden increase of the amplitude of the ASSR.^{3,4}

These observations raise the possibility that the marked attenuation of the ASSR by anesthetics reflects a disturbance of the central processes that mediate consciousness. It is just as likely, however, that attenuation of the ASSR and impairment of consciousness are distinct, unrelated effects, despite the common susceptibility to suppression by general anesthetics. The apparent link between ASSR attenuation and unconsciousness could be accounted for by the complete suppression of

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the ASSR by anesthetics at concentrations just sufficient to cause unconsciousness.

We evaluated the effect of isoflurane on the ASSR in the concentration range in which loss of consciousness occurs. Our goals were to characterize the isoflurane-ASSR concentration-effect relations and to evaluate the ability of the ASSR to predict the level of consciousness. A pilot study revealed that consciousness was lost between 0.26% and 0.50% during a very slow induction with isoflurane (0.02% every 3 min starting at 0.15%). Thus, we chose the following end-tidal concentrations: 0.26%, 0.38%, and 0.50%.

Methods

Participants

After approval of the Royal Victoria Hospital Ethics Board, we recruited 12 paid volunteers aged 20–31 yr (mean, 24 yr) who were classified as physical status 1 by the American Society of Anesthesiologists. We obtained written consent from the volunteers after providing detailed information about the risks of the study. The participants had no history of neurologic or hearing disorders. Results of otoscopy and of pure tone audiometry (portable audiometer model MA 40; Maico Hearing Instruments, Minneapolis, MN) were normal. Excess cerumen was removed in a few of the volunteers at the initial visit (more than 1 week before testing).

Anesthesia

After placement of the electroencephalograph (EEG) leads, we administered sodium citrate (0.3 M; 30 ml orally; BDH, Toronto, Ontario, Canada) and inserted an intravenous cannula under local anesthesia and attached the electrocardiograph leads, a noninvasive blood pressure monitor, and a pulse oximeter probe. The participants breathed oxygen (fresh gas flow, 6 l/min) *via* a circle system connected to an airtight clear face mask for 10 min to become familiar with the equipment. The inspired and expired concentrations of oxygen, carbon dioxide, and isoflurane were measured using a Datex Ultima monitor (Datex Instrumentarium, Helsinki, Finland) calibrated before each case with gas samples supplied by the distributor (Puritan Bennett, Pickering, Ontario, Canada). After baseline recordings of the ASSR, isoflurane (Ohmeda, Mississauga, Ontario, Canada) was administered with manual titration of the inspired concentration to reach the target end-tidal concentration. The participants breathed spontaneously. Each concen-

tration was kept constant for 15 min before the start of the recordings to allow equilibration of partial pressures between the brain and the lungs. The inspiratory oxygen fraction (Fi_{O_2}) remained > 0.96 , confirming that the mask was airtight.

Auditory Steady State Response and Level of Consciousness

Recordings of the ASSR were obtained during the following periods: at baseline, at each end-tidal isoflurane concentration (0.50%, 0.38%, and 0.26%, in that order) and at recovery (15 min after the end of isoflurane administration; nine participants only). Restlessness (two participants) and nausea (one participant) prevented recording during recovery. After equilibration of isoflurane partial pressures, recording required 12–15 min per period. A recording with the earphone disconnected (no stimulus) was also obtained during baseline to estimate residual EEG noise. The order of concentrations was chosen to allow data acquisition for another study of the effects of 0.26% isoflurane on cerebral potentials evoked by speech sounds. That study, which will be reported separately, required 20 min and was conducted after the 0.26% isoflurane ASSR recordings.

A microcomputer (using a Pentium microprocessor, Intel, Santa Clara, CA) equipped with two analog-to-digital/digital-to-analog cards (DT2821 series, Transduction, Mississauga, Ontario, Canada) was used to deliver stimuli and to record the EEG. Stimuli were 500-Hz tonebursts (10 ms; 82-dB peak equivalent sound pressure level) delivered to the right ear *via* insert-earphones ("E-A-R TONE" 3A; Cabot, Indianapolis, IN) at the rate of 35, 40, or 45 stimuli/s. For each participant, the stimulus rate yielding the largest response was determined before the baseline recordings and was used for all recordings. An insert-earphone without sound was placed in the left ear to partially block ambient noise.

The level of consciousness was assessed every minute during the recording periods. Consciousness was defined as responsiveness to verbal commands ("open your eyes" and "squeeze my fingers"). A volunteer who obeyed either or both commands was considered conscious. The commands were presented with a switch-activated microphone-amplifier connected to the earphone placed in the volunteer's right ear. The commands and the stimuli for producing the ASSR were never presented at the same time. For each assessment, the commands were repeated three times with increasing loudness from the normal conversation level to moderately forceful. The commands were presented in a

similar manner throughout the study. For the "squeeze my fingers" command, the investigator placed his finger in the participant's palm well before the verbal commands to distinguish reflex grasping to tactile stimulation from genuine response to verbal commands.

The EEG was recorded with gold-cup electrodes filled with conductive gel and fixed to the scalp with cotton gauze and collodion. The electrodes formed a coronal montage (T7, C5, C3, Cz, C4, C6, and T8⁵) with the right mastoid as a reference. Interelectrode impedances were less than 3 k Ω . The signal was amplified with a bandpass of 0.1 to 100 Hz (half amplitude; model 12A5 amplifiers, Grass Instrument, Quincy, MA). The analog-to-digital conversion rate was 1,120, 1,280, or 1,440 Hz to obtain 32 points per epoch that lasted 28.6, 25, or 22.2 ms for the 35-, 40-, and 45-stimulus/s rate. The epoch lasted one ASSR cycle. Epochs contaminated by artifacts ($\pm 100 \mu\text{V}$) were rejected automatically. For each period, we obtained nine replicate averages of the responses to 2,000 stimuli (with replacement of responses automatically rejected; 18,000 stimuli per period).

Data Validation and Reduction

Off-line inspection revealed that the data from two volunteers consisted primarily of myogenic potentials. The scalp distribution of these potentials suggested that the source was the temporalis muscle.⁶ The data from these volunteers were excluded from further analysis. We evaluated off-line the replicate averages of the remaining 10 volunteers (aged 20–29 yr; mean, 23 yr). For each volunteer and period, we excluded the replicate averages that clearly were deviant from the others. The number of discarded replicate averages was 19 (of 390 [5%]), and the maximum per volunteer for any period was two. The replicate averages were combined for each period and each volunteer to form a single tracing based on responses to 14,000–18,000 stimuli. The amplitude and the phase (relative to stimulus onset) of the ASSR were derived from Fast Fourier Transformation⁷ of those single averaged tracings.||

One volunteer awoke during recording of the fifth replicate average during the 0.50% period. He became very agitated and no further recording could be obtained at the 0.50% concentration. He became cooperative only when the concentration of isoflurane was reduced. The

four replicate waveforms obtained during the 0.50% period before his awakening were combined to form a single tracing based on 8,000 stimuli and processed as described already.

Statistical Analysis

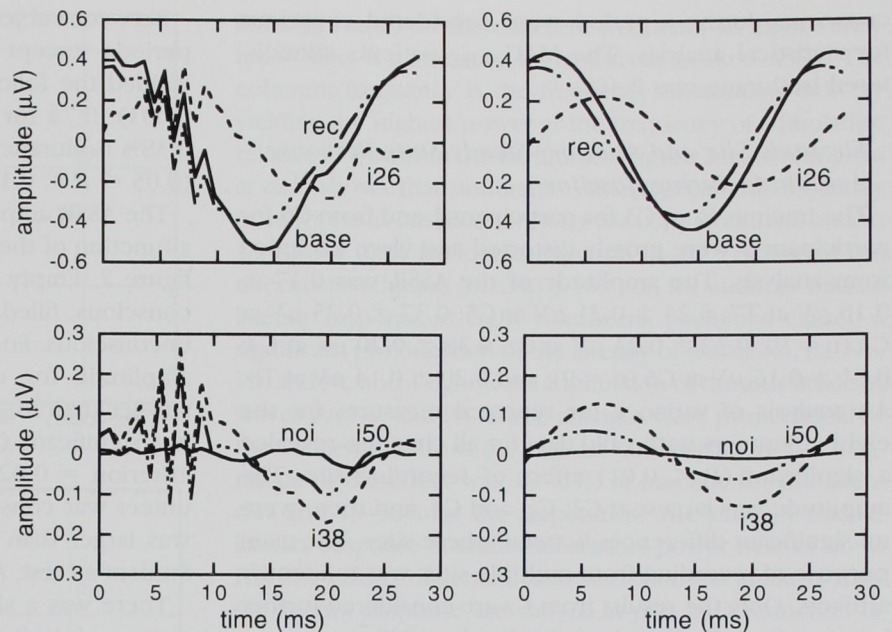
The procedures were performed using the program Statistica (version 4.1 for Macintosh; StatSoft, Tulsa, OK), unless otherwise indicated. We used logarithmic transformation when necessary to meet the assumption of normal distribution. The Lilliefors test⁸ was performed using the program Systat (version 5.2.1 for Macintosh; SPSS, Chicago, IL). Differences between recording periods were evaluated using analysis of variance for repeated measures. All periods were included except recovery. We adjusted the degrees of freedom with the Geisser-Greenhouse procedure. Tukey's Honest Significant Difference Test was used for *post hoc* comparisons.⁹ To compare recovery with the other periods, we chose paired Student's *t* tests in lieu of analyses of variance, which would have necessitated exclusion of the two volunteers with no data for recovery. Student's *t* test for unrelated samples was used to compare the amplitude of the ASSR for conscious and unconscious volunteers at the 0.38% concentration. Because only one volunteer was conscious at the 0.50% concentration, a one-sample Student's *t* test¹⁰ was used to compare that participant with the nine others.

Determination of phase coherence is a sensitive tool to assess the reliability of steady state responses.¹¹ For each period, we calculated phase coherence within and between subjects to determine objectively whether the ASSR was present. For within-subject analyses, we used the replicate averages, each based on 2,000 stimuli. For between-subject analyses, we used each volunteer's individual tracing (based on 14,000–18,000 stimuli) as the replication unit. Phase coherence (*C*) is defined as $C = [(\text{average sine})^2 + (\text{average cosine})^2]^{1/2}$, where sine and cosine are those of the phase at frequency of stimulation (35, 40, or 45) of the replicate averages (within-subject analysis) or of each volunteer (between-subject analysis). The Rayleigh test,¹² implemented in the C programming language (version 6.0 for DOS; Microsoft, Redmond, WA), was used to determine whether the level of phase coherence exceeded chance level.

We fitted the function $[\log(\text{ASSR amplitude}) = a \cdot \text{concentration} + b]$ by least-squares linear regression. All periods were included except recovery, for which the concentration of isoflurane was not recorded. We used dummy coding with multiple linear regression as neces-

|| Amplitude is computed as $(a^2 + b^2)^{1/2}$ where *a* and *b* are the real and imaginary Fast Fourier Transformation terms. Phase is the four-quadrant inverse tangent of *b/a*.

Fig. 1. Waveforms from one volunteer. The stimulus rate was 35/s. The amplitude scale of the lower panels is half that of the upper panels. (Left) Each trace is the average response to 14,000–18,000 stimuli. Base = baseline; i26, i38, and i50: isoflurane target concentration of 0.26%, 0.38%, and 0.50%, respectively; rec = recovery; noi = residual electroencephalographic noise estimated from a recording obtained during baseline with no auditory stimuli. Continuous lines = base and noi; dashed lines = i26 and i38; long-dashed/dotted lines = rec and i50. The fast waves from 4–8 ms represent the auditory brain stem response, which is distorted because of the amplification low-pass filter. (Right) Best-fit sinusoid for each trace to show the amplitude of the response for each period. Measuring the amplitude of the auditory steady state response by Fast Fourier Transformation is analogous to fitting a sinusoid.



sary for repeated measures design.¹³ Nonlinear (sinusoid) curve fitting for figure 1 was performed with the Levenberg-Marquardt algorithm⁷ using KaleidaGraph (version 3.08 for Macintosh computers; Synergy Software, Reading, PA).

We adopted the prediction probability (P_k) method of Smith *et al.*^{14,15} (implemented in Excel version 5 for Macintosh computers, Microsoft) and receiver-operating characteristic analysis¹⁶ to quantify the ability of the amplitude of ASSR or of the measured concentration of isoflurane to predict responsiveness to verbal commands. The P_k is a nonparametric, rank-order measure of association, ranging from 0.5 (chance level) to 1.0 (perfect concordance). The P_k value was based on 30 or 48 observations, depending on whether the baseline and recovery periods were excluded. We calculated the standard error of the estimate using the jackknife approach, as if the observations were independent, as performed by Leslie *et al.*¹⁷ Receiver-operating characteristic analysis is a method to quantify the performance of a volunteer or of a tool in indicating, based on indirect information, which of two events or states exists.¹⁶ A receiver-operating characteristic curve is a plot of the rate of true-positives (correctly detected events) as a function of the rate of false-positives (nonexisting events incorrectly classified as present) for all values of the decision criterion. Logistic regression with maximum likelihood estimation was used to estimate the minimum alveolar concentration for consciousness (MAC_{awake}) isoflurane.¹⁸

Results are expressed as mean \pm SD. The criterion for statistical significance was 0.05. Bonferroni correction was used for multiple Student's *t* tests. Correction is not necessary for Tukey's honest significant differences test.⁹ Applying Bonferroni correction to the tests of phase coherence would have been too conservative because of the large number ($n = 53$) of tests. To reduce the likelihood of spurious significance, we reduced the criterion to 0.01 for phase coherence testing.

Results

Level of Consciousness

In most instances, the volunteers either followed or ignored both verbal commands ("open your eyes" and "squeeze my fingers"). On rare occasions, a few volunteers obeyed only the command to open their eyes. In these instances, the volunteers were considered conscious.

The number of subjects who remained unconscious during the entire period was 0, 4, and 9 for 0.26%, 0.38%, and 0.50% isoflurane, respectively. The number of volunteers who remained conscious during the entire period was 10, 3, and 0 for 0.26%, 0.38% and 0.50% isoflurane, respectively. The number of volunteers who were intermittently conscious during the period were 0, 3, and 1 for 0.26%, 0.38%, and 0.50% isoflurane, respectively. The volunteers who were always or intermittently

conscious during a period were considered conscious for statistical analysis. The MAC_{awake} patients administered isoflurane was 0.40%.

Electrode Site and Auditory Steady State Response Amplitude during Baseline

The tracings from C3 for participant 1 and from C6 for participant 9 were grossly distorted and were excluded from analysis. The amplitude of the ASSR was $0.17 \pm 0.16 \mu\text{V}$ at T7; $0.24 \pm 0.21 \mu\text{V}$ at C5; $0.37 \pm 0.25 \mu\text{V}$ at C3 ($n = 9$); $0.32 \pm 0.23 \mu\text{V}$ at Cz; $0.38 \pm 0.20 \mu\text{V}$ at C4; $0.31 \pm 0.16 \mu\text{V}$ at C6 ($n = 9$); and $0.20 \pm 0.14 \mu\text{V}$ at T8. An analysis of variance for repeated measures for the eight volunteers with valid data for all channels revealed a significant ($P < 0.01$) effect of recording site. The amplitude was largest at C3, Cz, and C4, and there were no significant differences between these sites. The main purpose of recording from multiple sites was to identify artifacts. Only the results from Cz are considered further because Cz is the standard site for the ASSR.

Effects of Isoflurane on Auditory Steady State Response

The amplitude of the ASSR was $0.32 \pm 0.23 \mu\text{V}$ during baseline, $0.24 \pm 0.17 \mu\text{V}$ for 0.26% isoflurane, $0.09 \pm 0.05 \mu\text{V}$ for 0.38% isoflurane, $0.04 \pm 0.03 \mu\text{V}$ for 0.50% isoflurane, and $0.34 \pm 0.31 \mu\text{V}$ during recovery. The amplitude during baseline was significantly larger than during 0.38% ($P < 0.005$) and 0.50% isoflurane ($P < 0.001$). The amplitude during 0.26% isoflurane was significantly larger than during 0.38% ($P < 0.05$) and 0.50% isoflurane ($P < 0.001$). The amplitude during 0.38% isoflurane was larger than during 0.50% isoflurane ($P < 0.025$). The amplitude during recovery was significantly larger than during 0.38% and 0.50% isoflurane (Student's t tests; $P < 0.001$; Bonferroni criterion = 0.0125). The amplitude for recordings obtained without stimulus during baseline was $0.02 \pm 0.01 \mu\text{V}$. It was smaller than the amplitudes from all periods ($P < 0.001$) except 0.50% isoflurane ($P = 0.07$). Figure 1 shows tracings from one volunteer.

During all periods except 0.50% isoflurane, within-subject phase coherence was present for all volunteers (R from 0.80 to 0.98; $0.01 < P < 0.001$). During 0.50% isoflurane induction, six volunteers (including the one who regained consciousness during 0.50% isoflurane) showed phase coherence (R from 0.79 to 0.97; $0.01 > P > 0.001$). Four remaining volunteers showed no significant phase coherence, indicating that an ASSR could not be identified reliably (R from 0.19 to 0.63; $P > 0.05$).

Between-subject phase coherence was present for all periods except 0.50% isoflurane. The Rayleigh test yielded the following R values: 0.82 for baseline ($P < 0.001$), 0.74 for 0.26% isoflurane ($P < 0.01$), 0.80 for 0.38% isoflurane ($P < 0.001$), 0.52 for 0.50% isoflurane ($0.05 < P < 0.10$), and 0.90 for recovery ($P < 0.001$).

The ASSR amplitudes for each volunteer are shown as a function of the end-tidal concentration of isoflurane in figure 2. Empty circles indicate that the volunteer was conscious; filled circles indicate that the volunteer was unconscious. For the target concentration of 0.38%, the amplitude for unconscious volunteers tended to be smaller than for conscious ones, but the difference was not significant (Student's t test; $P = 0.16$; Bonferroni criterion = 0.025). For the 0.50% target, only one volunteer was conscious. The amplitude for that volunteer was larger than for the unconscious ones (one-sample Student's t test, $P < 0.01$; Bonferroni criterion = 0.025).

There was a significant relation between the concentration of isoflurane and the amplitude of the ASSR. Linear regression for the equation $[\log(\text{ASSR amplitude}) = a \cdot \text{concentration} + b]$ yielded $r = 0.85$ ($P < 0.0001$). The parameters a and b were -0.460 and -1.804 .

Prediction of the Level of Consciousness

Figure 3 shows the receiver-operating characteristic curves for ASSR and the measured concentrations of isoflurane (0.24 to 0.57%). Perfect sensitivity (the true-positive rate of 1) was associated with a false-positive rate of 0.15 for ASSR and 0.40 for concentration. The P_k values based on the 0.26%, 0.38%, and 0.50% periods were 0.950 (SE 0.044) for the ASSR amplitude and 0.948 (SE 0.036) for the observed end-tidal concentration of isoflurane. The P_k value based on all periods, including recovery, was 0.970 (SE 0.028) for the ASSR amplitude. The equivalent P_k value for the concentration of isoflurane is not available because the concentration of isoflurane was not recorded during recovery.

Discussion

The results indicate that the ASSR is attenuated in a concentration-dependent manner by isoflurane; that profound attenuation of the ASSR and loss of consciousness (defined as loss of responsiveness to verbal commands) occur in the same end-tidal concentration range; that both ASSR and end-tidal concentration are very good predictors of the level of consciousness; and that an ASSR amplitude $< 0.07 \mu\text{V}$ always is associated with unconsciousness.

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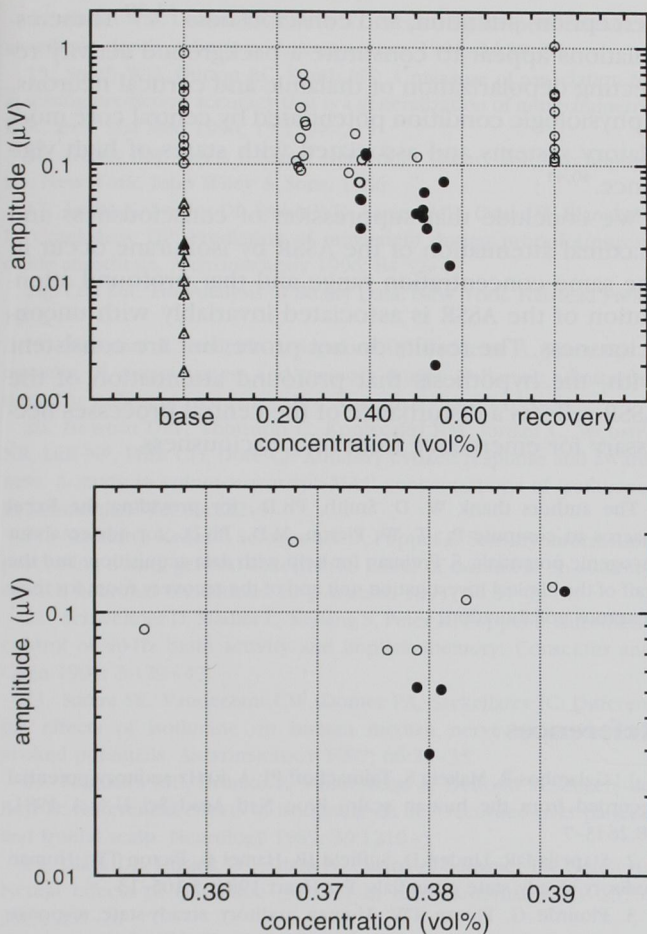


Fig. 2. (Top) The auditory steady state response amplitude (log scale) as a function of the measured end-tidal concentration of isoflurane. Empty circles indicate measures obtained when the volunteers were conscious; filled circles indicate measures obtained when the subjects were unconscious. The triangles show residual electroencephalographic noise estimated from recordings obtained during baseline with the earphone disconnected. These triangles delimit the range of expected amplitudes if the auditory steady state response is abolished. Because many points overlap at the 0.38% isoflurane target concentration, an expanded view of these results is shown in the lower portion of this figure. The 0.001 value at the bottom left is a y-axis (amplitude) label. It does not pertain to the isoflurane concentration. (Bottom) An expanded view of the 0.38% isoflurane target concentration data.

How does the ASSR compare with other neurophysiologic measures of anesthetic effect? The measures for which the effect of a low concentration of isoflurane has been well documented are the coherent frequency of the auditory evoked response, the auditory middle latency response, the median nerve somatosensory evoked potential, the unprocessed EEG, and the spectral and bispectral analysis of the EEG.

Munglani *et al.*¹⁹ studied the effect of isoflurane (0.2 to

0.8% end-tidal) on the coherent frequency in eight volunteers. This is a measure derived from evoked ASSR. The coherent frequency is the frequency of stimulus delivery yielding the highest power at the frequency of stimulation relative to power in the harmonics. Figure 2 from Munglani *et al.*¹⁹ shows that isoflurane reduced coherent frequency from 33 Hz at baseline to 24 Hz for 0.4% isoflurane and to 15 Hz for 0.8% isoflurane. Newton *et al.*²⁰ evaluated the effects of isoflurane (0.12 to 0.46%) on the auditory middle latency response in eight volunteers. Isoflurane caused a significant prolongation of the latency of waves Na, Pa, Nb, Pb, and Nc and a significant attenuation of the amplitude of waves Pa, Nb, and Pb. These changes were proportional to the concentration. At the highest concentration, the magnitude of the effect was 18–23% of baseline for the latencies and 45–58% for the amplitudes. The auditory middle latency response contains substantial power near or at 40 Hz. The effects of general anesthetics on the auditory middle latency response are caused in part by a reduction of the components near or at 40 Hz.^{21,22} Isoflurane, 0.5%, end-tidal in oxygen decreased by 50% the amplitude of the parietal N20 wave and the standard reference wave of the somatosensory evoked potential and increased latency by 1 ms.^{23,24}

Clark *et al.*²⁵ evaluated the effect of isoflurane on the unprocessed EEG. They studied four conscious persons exposed to 0.18–0.30% end-tidal isoflurane. The EEG showed a loss of α band (8–12 Hz) activity with replace-

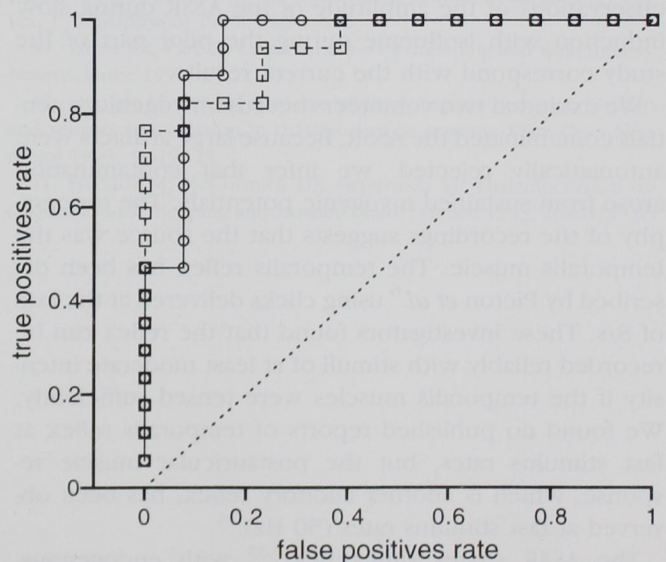


Fig. 3. Receiver-operating characteristic curve for the auditory steady state response amplitude (circles) and measured isoflurane concentration (squares). The dotted line represents chance level. The farther the receiver-operating characteristic curve from the dotted line, the better the performance.

ment by low-amplitude fast activity with a frequency of 15- to 35-Hz bursts. These authors also studied two unconscious persons during 0.78–0.79% isoflurane. The EEG showed 12- to 14-Hz low-amplitude activity superimposed on 2- to 6-Hz high-amplitude waves. Dwyer *et al.*²⁶ evaluated the effect of isoflurane (0.15, 0.30, and 0.45 MAC, age adjusted) on various spectral parameters of the EEG in 12 persons. These investigators found two significant changes relative to awake baseline: a modest increase of the median power frequency at the 0.30 and 0.45 MAC levels and an increase of absolute power in the α -band at the 0.45 MAC level.

Glass *et al.*²⁷ evaluated the effects of isoflurane (0.25, 0.50, 0.75, and 1.00%) on the bispectral index of the EEG in 10 persons. Isoflurane decreased this index in a linear, concentration-dependent manner. Isoflurane, 0.50%, reduced the bispectral index by approximately 35% of baseline, based on figure 1 of Glass *et al.*²⁷ The P_k score for consciousness was 0.96 for the bispectral index and 0.97 for the measured concentration of isoflurane. These values are similar to those of the current study.

We obtained a MAC in awake patients of 0.40%. This is within the range of reported values (0.32 to 0.50%).^{20,27–30} We used the same order of concentrations for all volunteers to conduct another study at the 0.26% isoflurane level. It would have been better to balance the concentration order among volunteers, but we do not think that the results would have differed. Our observations of the amplitude of the ASSR during slow induction with isoflurane during the pilot part of the study correspond with the current results.

We excluded two volunteers because myogenic potentials contaminated the ASSR. Because large artifacts were automatically rejected, we infer that contamination arose from sustained myogenic potentials. The topography of the recordings suggests that the source was the temporalis muscle. The temporalis reflex has been described by Picton *et al.*⁶ using clicks delivered at the rate of 8/s. These investigators found that the reflex can be recorded reliably with stimuli of at least moderate intensity if the temporalis muscles were tensed sufficiently. We found no published reports of temporalis reflex at fast stimulus rates, but the postauricular muscle response, which is another auditory reflex, has been observed at fast stimulus rates (50 Hz).³¹

The ASSR shares similarities^{32,33} with endogenous, spontaneously occurring 40 Hz or γ -band (25–80 Hz) oscillations, which are the subject of much contemporary research because of their association with states of high vigilance^{34–36} and their possible role in sensory

perception, attention, and consciousness.^{37–39} These oscillations appear to constitute a background activity reflecting depolarization of thalamic and cortical neurons, a physiologic condition potentiated by central core modulatory systems and associated with states of high vigilance.^{40,41}

We conclude that suppression of consciousness and maximal attenuation of the ASSR by isoflurane occur in the same concentration range and that profound attenuation of the ASSR is associated invariably with unconsciousness. The results do not prove, but are consistent with, the hypothesis that profound attenuation of the ASSR reflects a disturbance of the central processes necessary for emergence from unconsciousness.

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