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HUMAN AUDITORY STEADY-STATE RESPONSE, ELECTROENCEPHALOGRAM, AND LATE AUDITORY EVOKED POTENTIALS DURING GENERAL ANESTHESIA

Gilles Plourde M.D.

Dissertation

presented to the Department of Physiology

at the Faculty of Medicine

of the University of Ottawa

in partial fulfillment of the

requirements for

the degree of Master of Sciences.

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UNIVERSITÉ D'OTTAWA
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A B S T R A C T

In order to identify neurophysiological correlates of the changes in the level of conciousness associated with general anesthesia, the 40 Hz auditory steady-state response (ASSR), the electroencephalogram (EEG) and the N1 and P3 components of the transient auditory evoked potential were recorded before anesthesia (pre-induction), at the onset of anesthesia (induction), during surgical anesthesia, at the time of emergence (the first 10 min. after the return of patients's responsiveness) and during recovery from anesthesia (the following 2-3 hours). Fourteen healthy patients undergoing elective surgery were tested. The anesthetic agents were thiopental, fentanyl and isoflurane with (7 patients) or without (7 patients) nitrous oxide. The ASSR was produced by 500 Hz tones delivered at 40 sec^{-1}. The transient auditory evoked potentials were produced by 700 Hz tones that occurred unpredictably in the train of 500 Hz tones. The patients were required to press a button following each 700 Hz tone whenever possible. The responses evoked by detected 700 Hz tones (hits) were compared with those evoked by undetected 700 Hz tones (misses). The amplitude of the ASSR, measured in the frequency domain, was reduced significantly during late induction and dropped below noise levels during surgical anesthesia. It increased during emergence and further increased during recovery although the amplitude during recovery was significantly less than pre-induction values. Total EEG power increased significantly after induction. The EEG median frequency and 95% quantile frequency decreased significantly during surgery and increased significantly

during emergence. Muscle artifacts could account for many of the EEG changes. The results for the transient auditory evoked potential indicated that, except during emergence, hits were associated with clear N1 and P3 waves whereas misses were not. The lack of either N1 or P3 for hits during emergence perhaps occurred because the patients were not yet fully conscious despite their ability to perform a simple detection task. In conclusion, the amplitude of the ASSR provides a good indicator of the level of arousal. The usefulness of the EEG is limited by muscle artifacts. The N1 and P3 components of the auditory evoked potential reflect changes in the level of consciousness during general anesthesia.

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L I S T O F T A B L E S

L I S T O F F I G U R E S

LIST OF ABBREVIATIONS

ABR	auditory brainstem response
AD	analog-to-digital
ASSR	auditory steady-state response
CO_2	carbon dioxide
C_z	10-20 system scalp location (vertex)
EEG	electroencephalogram
EP	evoked potential
F_z	10-20 system scalp location (frontal, sagittal mid-line)
M_1	left mastoid
M_2	right mastoid
MAC	minimum alveolar concentration
N_2O	nitrous oxide
P_z	10-20 system scalp location (parietal, sagittal mid-line)
REM	rapid eye movement (sleep stage)
s	second
SD	standard deviation
SPL	sound pressure level

A C K N O W L E D G E M E N T S

I express my profound gratitude to Terry Picton for his enthusiastic and very generous support. Adrian Kellett and Dick Mowrey provided essential and friendly technical and programming assistance respectively. Members of the Royal Victoria Hospital Anaesthesia Department provided optimal conditions for conducting this research. Ms. Susan Caney provided superb secretarial assistance. These studies were supported by a fellowship from the Fonds de la Recherche en Santé du Québec.

I N T R O D U C T I O N

It is difficult to define the concept of "level of anesthesia". The levels of anesthesia were originally based on the changes of somatic and autonomic signs during anesthesia with diethyl ether. These signs reflected both the progressive impairment of central nervous system functions as well as the direct effects of the anesthetic agent on other organs (heart, blood vessels...). The pattern of change was consistent across patients and marked different clinical levels of anesthesia (Guedel, 1937, Gillespie, 1945). These elaborate scoring systems lost most of their usefulness with the introduction of new anesthetic agents (Guedel, 1940; Clark and Rosner, 1973). The evaluation of level of anesthesia then faced so many inconsistencies that Galla et al. (1958) considered whether or not the concept of level of anesthesia should be abandoned.

Since the goals of general anesthesia are unconsciousness (and amnesia), analgesia and muscle relaxation, an alternative approach is to use somatic and autonomic signs to evaluate these goals (Grantham and Hameroff, 1985; Evans, 1987). Responsiveness to sensory stimulation is used to assess the level of consciousness or arousal and (when the stimuli are painful) the quality of analgesia. Muscle relaxants and autonomic drugs, frequently used in current anesthesia practice, unfortunately interfere with the evaluation of a patient's responsiveness (Evans, 1987). There is therefore a great need for a physiological measure that varies with the level of responsiveness without being affected by muscle relaxants or autonomic agents.

The scalp-recorded electroencephalogram (EEG) has been used extensively to study the effects of anesthetic agents on the brain and to monitor the level of anesthesia. The EEG is the result of summated post-synaptic potentials (Creutzfeldt et al., 1966). Anesthetic agents produce dose-dependant EEG changes (Clark and Rosner, 1973; Levy et al., 1980; Stockard and Bickford, 1981; Pichlmayr et al., 1984). Despite similarities between different agents, these effects are agent-specific (Martin et al., 1959; Clark and Rosner, 1973; Stockard and Bickford, 1973). Interpretation of the EEG patterns is difficult, particularly when multiple agents are combined and when body temperature or the arterial partial pressure of CO_2 vary. A particular EEG pattern does not signal the same clinical state for different agents. The EEG therefore does not provide a uniform measure of the level of anesthesia (Martin et al., 1959; Robson, 1965; Clark and Rosner, 1973; Stockard and Bickford, 1981). Nevertheless many authors consider that the EEG changes produced by most anesthetic agents are sufficiently comparable to warrant the use of the EEG for monitoring the level of anesthesia (Bimar and Bellville, 1977; Kugler, 1981; Sebel et al., 1981; Smith et al., 1984; Prior, 1987; Stoeckel and Schwilden, 1987).

The EEG has limited usefulness for evaluation of the level of consciousness during anesthesia. The EEG may sometimes indicate that a patient is unconscious (e.g. burst suppression or isoelectricity), but it cannot indicate when and if a patient is conscious (Clark and Rosner, 1973; Stockard and Bickford, 1981; Hug, 1985; Prior, 1987; Mori, 1987). An alpha pattern, similar to the normal alpha rhythm of conscious subjects, can be seen in anesthet zed patients and widespread delta activity, similar to that seen in sleep, anesthesia or coma, can be seen in conscious patients (Robson, 1965; Sharbrough, 1987). In general the

EEG patterns seen with most current anesthetic regimens do not provide information about the level of consciousness (Robson, 1965).

Scalp-recorded sensory evoked potentials (EPs) may possibly provide more specific information about the level of anesthesia. EPs are changes of the ongoing EEG produced by sensory stimuli. The auditory and somatosensory modalities are most often used in studies of anesthesia. (It is difficult to maintain a consistent visual stimulus during anesthesia). Sensory EP consists of a series of positive or negative peaks. Peaks of the auditory EP can be classified on the basis of post-stimulus latency as early (0-8 ms), middle (8-50 ms) and late (60-500 ms) (Picton and Hillyard, 1974). Peaks of the somatosensory EP can be similarly classified although the latencies are longer because the stimuli must pass through the peripheral nervous system.

Anesthetic agents change the sensory EPs. These changes vary with the sensory modality, the individual peak, the anesthetic agent and various physiological variables (Clark and Rosner, 1973; Stockard and Bickford, 1981). The middle latency peaks of the auditory and somesthetic EP show dose-related amplitude reductions with general anesthetics (Jones, 1987). In the auditory modality surgical stimulation can reverse these changes (Jones, 1987).

Evoked potentials can be classified as transient or steady-state responses. With transient EPs the rate of stimulation is sufficiently slow that the response is over before the next stimulus occurs. Generation of a steady-state response requires a faster rate of stimulation which results in the superimposition of individual responses to form a sustained, sinusoidal response which has a frequency equal to the rate of stimulation. Transient responses are usually described in terms of the amplitude and latency of their peaks whereas steady-state

responses are described by their amplitude and phase relative to stimulus onset (Regan, 1989). Evoked potential studies during anesthesia have generally focused on the short and middle latency components of transient responses. The auditory steady-state response (ASSR) (Stapells et al., 1984; Picton, 1987) is largest for stimulus rates of about 40 Hz (Galambos et al., 1981). Reducing the stimulus intensity decreases the amplitude of the response and increases the phase (Picton, 1987).

Several features of the ASSR make it a possible candidate for use in monitoring anesthesia. The ASSR is a steady-state equivalent of the transient middle latency response (Galambos et al., 1981) which shows graded, dose-related amplitude reduction with general anesthetics (Jones, 1987). The amplitude of the ASSR is reduced by 50% during sleep (Linden et al., 1985; Jerger et al., 1986; Picton, 1987). Studies of normal subjects (Galambos and Makeig, 1988) have shown spontaneous fluctuations in the amplitude of the response over approximately one minute that apparently relate to concomitant fluctuations in general arousal. Changes in the level of waking attention do not, however, affect the ASSR, (Linden et al., 1987) a feature which might be useful in the peri-anesthetic period. Preliminary results have indicated that the amplitude of the ASSR is substantially reduced during general anesthesia (Hogan, 1987).

In Experiment 1 we have recorded the 40 Hz ASSR before, during and after general anesthesia (thiopental, fentanyl, isoflurane with or without nitrous oxide) to examine the relationship between the response and the level of arousal during the various stages of the procedure (pre-induction, induction, surgical anesthesia, emergence and recovery from anesthesia). We have also recorded the EEG for comparison with the

ASSR results. The recording protocol was first validated in unanesthetized subjects.

Evoked potentials can also be classified as exogenous or endogenous (Picton and Hillyard, 1988). Exogenous EPs are mainly influenced by the physical nature of the evoking stimulus. They have frequently been recorded during anesthesia (Sebel et al., 1985; Jones, 1987). Endogenous EPs generally occur after 100 ms, are sensitive to the psychological state of the subject and are relatively independent of the physical nature of the stimulus. Endogenous EPs have a well established role in the study of human cognition (Hillyard and Kutas, 1983; Hillyard and Picton, 1987; Picton and Hillyard, 1988). They may provide better assessment of the changes of the level of conciousness associated with general anesthesia. Adequate assessment of the level of consciousness is important because intra-operative awareness may occur (incidence : 2-3%) and cause psychological trauma (Bitner, 1983). Two components of the transient auditory evoked potential were considered for monitoring the level of conciousness: the N1 and the P3 (or P300).

The N1 auditory EP has a peak latency of 100 ms and is maximally recorded at the vertex. It displays some exogenous characteristics, being larger for more intense stimuli. The N1, however, has some endogenous characteristics in that it varies with selective attention (Hillyard nad Picton, 1987; Näätänen and Picton, 1987). When a subject is instructed to pay attention to stimuli presented to one ear and to ignore stimuli presented to the other ear the amplitude of the N1 is larger for stimuli presented to the attended ear. These changes with attention may in part be related to the superimposition of a separate "processing negativity" on the N1 wave. In tasks where the subject only attends to one train of stimuli and the discriminations are easy there

is usually no effect of attention on the N1.

The P3 (or P300) is a parietocentral positive wave with a typical peak latency of 300 ms (range 250-600 ms) (Pritchard, 1981). It is associated with the conscious detection of "target" stimuli and is independent of the sensory modality. The most common paradigm for eliciting the P3 requires the subject to attend to a train of regularly occurring stimuli in order to detect improbable, unpredictable target ("oddball") stimuli that differ from the standard stimuli (e.g. occasional high-frequency tones in a run of low-frequency tones). Requiring the subject to count or to press a button in response to the targets is sufficient to elicit a P3. By contrast the P3 is very small or absent when the subject ignores the targets. Several investigators have suggested that the P3 is associated with access to consciousness (Pritchard, 1981; Donchin et al., 1983; Picton and Hillyard, 1988).

Two types of P3 have been described (Squires et al., 1975). The P3a has a typical latency of 250 ms, and a frontal scalp-distribution. It occurs following improbable stimuli whether or not the subject is attending to the stimulus sequence and probably reflects the recognition of mismatch between the probable and improbable stimuli. The larger P3b has a typical latency 300 ms, and a parietocentral scalp-distribution. It occurs when the subject is actively discriminating stimuli and may represent the actual processing of the detected mismatch.

In Experiment 2 we have recorded the late auditory EPs before, during and after general anesthesia in order to assess the relationship between the N1 and P3 and the level of consciousness. The recording paradigm was first evaluated in unanesthetized subjects.

EXPERIMENT 1

METHODS

Subjects

The project was approved by the Institutional Research Ethics Committee. Written informed consent was obtained from all subjects.

Ten normal unanesthetized subjects (7 males) participated in the initial control portion of the study. The mean age was 31 years (range: 23-43). All subjects were free from neurological or otological disease. They were tested in a sound-attenuated, electrically shielded room.

Ten patients (6 females) were then tested during elective surgery. The mean age was 34 years (range: 21-61). (Four other patients were tested but their response was inadequate because of an error in setting the recording parameters.) All patients were free from neurological or otological disease. Surgical procedures consisted of: plastic surgery (6 patients), orthopedic surgery (2 patients), urological surgery (one patient) and general surgery (one patient).

Anesthetic Technique

Eight patients were premedicated with diazepam (0.1 $mg.kg^{-1}$) by mouth 60-90 minutes pre-operatively. Two patients received no premedication. Anesthesia was induced with thiopental (5 $mg.kg^{-1}$). After loss of responsiveness, vecuronium (0.1 $mg.kg^{-1}$) was used to facilitate tracheal intubation. The lungs were mechanically ventilated to maintain the end-tidal CO_2 partial pressure at 30 mmHg (mass spectrometry). Fentanyl (3 $\mu g.kg^{-1}$) and isoflurane (0.5-1.5% end-tidal)

in oxygen (five patients) or in N_2O (60% end-tidal)/oxygen (five patients) were used for maintenance. Nasopharyngeal temperature was continuously monitored. Prostigmine (with glycopyrrolate) was used to reverse muscular paralysis prior to emergence.

Auditory Steady-state responses (ASSR)

Stimuli

Tonebursts (500 Hz, 15 ms duration, 5 ms rise/fall time, 90 dB peak sound pressure level (SPL)) were presented binaurally at a rate of 40 per second via TDH-49 earphones in the controls and via insert earphones (Etymotic Research, model ER3A) in the surgical patients. The frequency was occasionally (10 per minute on average) increased to 700 Hz for 75 ms to produce target stimuli. The patients were required to press a button following target stimuli whenever possible. With three patients, belonging to the isoflurane in oxygen group, additional ASSR were recorded with 100 dB peak SPL stimuli to evaluate the effect of intensity on the ASSR during anesthesia.

Recording

The EEG was recorded with gold-plated cup electrodes attached with saline gel and collodion. The inter-electrode impedances were less than 5 kOhms (10 Hz). Three electrodes were placed according to the International 10-20 system (Jasper, 1958) at frontal (Fz), central (Cz) and parietal (Pz) mid-sagittal scalp locations with the right mastoid (M2) as common reference. Vertical eye movements (EOG) (forehead-cheek) were also recorded. Half-amplitude lower and upper cut-offs were 0.16 and 100 Hz with a -20dB/decade roll-off. The amplifiers followed the EEG convention that negativity at the scalp relative to the reference was plotted upward.

The duration of the analog-to-digital (AD) sweep was 1490 ms. Sampling frequency was 688 Hz per channel. The interval between onset of AD sweeps was 2000 ms. The AD resolution was 12 bits. Sweeps contaminated by excessive muscle or eye movements were rejected. The rejection-level on all channels for the control subjects was $\pm$ 87.5 μV. For the anesthetized patients the rejection level was $\pm$ 175 μV. Less stringent rejection criteria were used with the anesthetized patients because EEG changes due to the anesthetic agents would have caused excessive rejection.

A recording block consisted of 45 AD sweeps (a duration of 90 s) for the control subjects and of 100 AD sweeps (200 s) for the surgical patients. Sweeps occurring in the first half of a recording block were averaged separately from those in the later half. This was done to increase the time resolution for recordings during induction.

Measurements

The responses were analyzed using time-and frequency-domain methods. For time-domain analysis, the waveforms were digitally filtered (38-42 Hz, extended cosine bell window) (Beauchamp and Yuen, 1979; Picton et al., 1984) and the root-mean-square amplitude (which is the standard deviation of the response) was measured. For frequency-domain analysis the amplitude and phase at 40 Hz were obtained from the fast Fourier transform of the unfiltered traces. The phase (sine wave) was measured at onset.

Auditory Brainstem Response (ABR)

In order to rule out significant conductive hearing loss during anesthesia ABRs were recorded before anesthesia and during surgery in

three patients (the same patients in whom the effect of stimulus intensity on the ASSR was tested).

Stimuli

Rarefaction clicks with an intensity of 95 dB peak SPL (equivalent to 60 dB above normal hearing threshold) and a duration of 0.1 ms were presented monaurally at a rate of 11.1 per sec.

Recording

Recording was from Cz-left mastoid (M1) and Cz-M2. Bandpass was 30-3000 Hz. Duration of AD sweep was 8 ms. Sampling frequency was 42.4 kHz per channel. Artifact rejection was set at $\pm$ 175 μV. Both ears were tested with at least three replications of 2000 sweeps. Replicate waveforms were combined and digitally filtered (50-2500 Hz) prior to measurements.

Measurements

Waves I, II and V were identified on the Cz-ipsilateral mastoid channel according to current clinical procedures (Am EEG Soc, 1984). The amplitudes were measured relative to the most negative succeeding peak or inflection within the next 1.5 ms..

Electroencephalogram (EEG)

Recording

The EEG was recorded for eight seconds after each recording block. Sampling frequency was 128 Hz. Recording parameters were otherwise similar to those used for recording the ASSR.

Adequate digital representation of an analog signal requires that the AD sampling rate be at least twice the highest frequency present in the signal (Beauchamp and Yuen, 1979). We used an AD sampling rate of 128 Hz with an amplifier upper cut-off of 100 Hz (required for the

recording of the ASSR). Thus, all signal frequencies above 64 Hz were represented in the low frequencies (aliasing) (Beauchamp and Yuen, 1979). This problem was minimal because (1) there was very little activity above 40 Hz in the signal as determined by inspection of the unfiltered EEG and (2) the frequency response curve for the amplifiers (Grass model P511K) already shows at least 25% attenuation at 50 Hz.

Measurements

The following measures were derived from the power spectrum: median (Stoeckel and Schwilden, 1987) and 95% quantile frequency ("spectral edge") (Hudson et al., 1983) as well as the average power in the delta (0.5-3.4 Hz), theta (3.5-7.4 Hz), alpha (7.5-13.4 Hz) and beta (13.5-30.0 Hz) frequency bands expressed as percentage of total power from 0.5 to 30.0 Hz. Determination of the median and 95% quantile frequencies was done after filtering the EEG from 0.5 to 32 Hz. The ratio (alpha + beta)/(delta + theta) was also computed. The choice of these measures was based on current trends in anesthesia EEG monitoring (Levy et al., 1980; Pichlmayr et al., 1984).

Design

Awake control subjects were initially tested to ensure that consistent responses could be obtained with the experimental protocol. The following five (A - E) conditions assessed the effects of attention, task and eye status (open/closed) on the ASSR. In Condition A the subjects kept their eyes closed, pressed a button following each target stimulus and counted the number of target stimuli. In condition B, the subjects kept their eyes closed and counted the number of target stimuli without pressing the button. In condition C, the subjects kept their eyes closed and pressed a button following each target stimulus without

counting the number of targets. Condition D was similar to Condition A except that the subjects kept their eyes open. For condition E, the subjects read a book and ignored the target stimuli. There were two recording blocks for each condition. The order of conditions and replications was counterbalanced within and across subjects. Recordings for each condition were combined prior to measurement.

With anesthetized patients recordings were obtained during the following periods: pre-induction (30-90 min before induction), induction, surgery, emergence and recovery. The patients kept their eyes closed and were instructed to press a button following each target whenever possible (similar to condition C above). The injection of thiopental began 15-30 sec after the beginning of the induction recording and lasted one minute. Data for the first 100 seconds of the induction recording (early induction) were averaged separately from those for the last 100 seconds (late induction). The recordings during surgery were done at stable (10 min) concentrations of isoflurane: 0.5% end-tidal when administered with 60% N_2O and 1.15% end-tidal when administered in oxygen alone. After surgery, the trachea was extubated as soon as the patients were able to obey simple commands. Emergence was defined as the 10 min period immediately following tracheal extubation and was followed by recovery. Within each period other than induction multiple recordings were carried out. Individual recordings from each period in each patient were combined prior to measurement. In contrast, EEG measurements were taken from individual recordings and were then averaged for each period. The effect of surgical stimulation was not evaluated because of cautery interference following skin incision. Recordings could not be obtained from all patients for all

periods because of patient-related factors such as movements and shivering.

Statistical Analysis

Rayleigh test for phase coherence and Hotelling's T^2 statistic (Picton et al., 1987) were used to determine if the response was consistent between subjects. The analysis was done separately for awake controls and anesthetized patients. The steady-state response from individual subjects may be represented as points in a two-dimensional space. The amplitudes and phases of the responses correspond respectively to the lengths and angles of the lines joining the points to the origin (zero point). When a response is present, the points will cluster in an area away from the origin. When only noise is present, the points will be around the origin. Hotelling's T^2 statistic measures the amplitude of the response relative to the variability of the measurements. Phase coherence is an amplitude-free test. It evaluates the range of angles subtended by the quiver of arrows originating at zero and pointing to the measurements.

Unpaired T-tests (one per period) were used to determine if results from patients of the isoflurane in O_2 group differed from those of the isoflurane in N_2O/O_2 group. There were no significant differences and the results from both groups were pooled. The results for awake controls and anesthetized patients were analyzed with one-way ANOVAs for repeated measures using the Geisser-Greenhouse adjustment of the significance levels and correction for missing values (Kirk, 1982; Dixon, 1985). Missing values (nine for the anesthetized patients and none for the controls) were replaced by the mean for the period. ANOVA-based planned comparisons and post-hoc tests (Scheffé's) were used with

controls (Kirk, 1982). Because of the missing values, paired t-tests were used (instead of ANOVA-based procedures) for comparisons in the patients. Each period was compared to the preceding period. Pre-induction was compared to surgery and recovery. One-tailed tests were used for the steady-state data. Two-tailed tests were used with EEG data because the direction of the changes could not always be predicted. Criterion for significance was $P < 0.05$ for the ANOVAs and $P < 0.01$ for paired comparisons.

R E S U L T S

Awake Controls

Table I shows the average amplitude and phase measurements. The amplitude for the IGNORE condition was slightly but significantly smaller than for the other conditions in both time-domain and frequency-domain. Although the difference was small the ANOVAs were significant ($P < 0.05$) and the paired comparisons of the IGNORE condition with all other conditions were significant ($P < 0.01$). The phase during the eyes-open conditions was slightly larger than during eyes-closed conditions. The ANOVA was significant ($P < 0.001$) and post-hoc tests showed that the difference between eyes-open versus eyes closed conditions was significant (Scheffé's test, $P < 0.01$).

Phase coherence and Hotelling's T^2 statistic showed that the responses were consistent between subjects ($P < 0.01$) for all conditions.

Average waveforms for all patients and the amplitude spectra are shown in Fig. 1. The 40 Hz activity is clearly visible on the unfiltered average waveforms as a sinusoidal pattern and on the amplitude spectra which show a clearly recognizable peak at 40 Hz relative to adjacent frequencies.

Anesthetized Patients

Anesthetic management

The average interval between induction and extubation was 126 min (SD 56). The recordings in the recovery room were started on average 38 min (SD 23; range; 10-65) after extubation and were completed 68 min (SD

31; range 27-114) after extubation. The mean nasopharyngeal temperature during surgery was 36.2°C. (SD 0.51; range 35.4-37.0). The mean end-tidal partial pressure of CO_2 during surgery was 29.3 mmHg (SD 2.0 range 27.1-32.3). For patients receiving isoflurane and N_2O, the mean end-tidal concentrations were respectively 0.57% (SD 0.12) and 61% (SD 8) (1.2 MAC). (MAC stands for the Minimum Alveolar Concentration of anesthetic agent at one atmosphere required to abolish movement in 50% of patients or animals in response to a noxious stimulus (Merkel and Eger, 1963). It is the most widely accepted measure to compare the potency of inhalation agents. The MAC of isoflurane in humans is 1.15% (Cullen, 1986).) For patients receiving isoflurane only, the mean end-tidal level was 1.04% (SD 0.08) (0.9 MAC).

Clinical evaluation of the level of consciousness revealed the following. During pre-induction, all patients were alert and awake. The transition from consciousness to unconsciousness generally occurred at the end of early induction. In three patients, the transition occurred at the beginning of late induction. During surgery, the patients were non-responsive and tolerated the surgical stimulation without tachycardia or hypertension. During emergence, the patients were very drowsy but they opened their eyes on command. During recovery the patients became progressively more alert. They remained, however, more somnolent than during pre-induction.

Steady-state responses

Average waveforms for all patients and the amplitude spectra are shown in Fig. 2. The amplitude spectra reveal a clearly recognizable peak of 40 Hz relative to adjacent frequencies during pre-induction, early induction and recovery. During late induction and emergence the

Table 1: AUDITORY STEADY-STATE RESPONSE - AWAKE CONTROL SUBJECTS

Mean and standard deviation (in brackets) for the 10 control subjects.

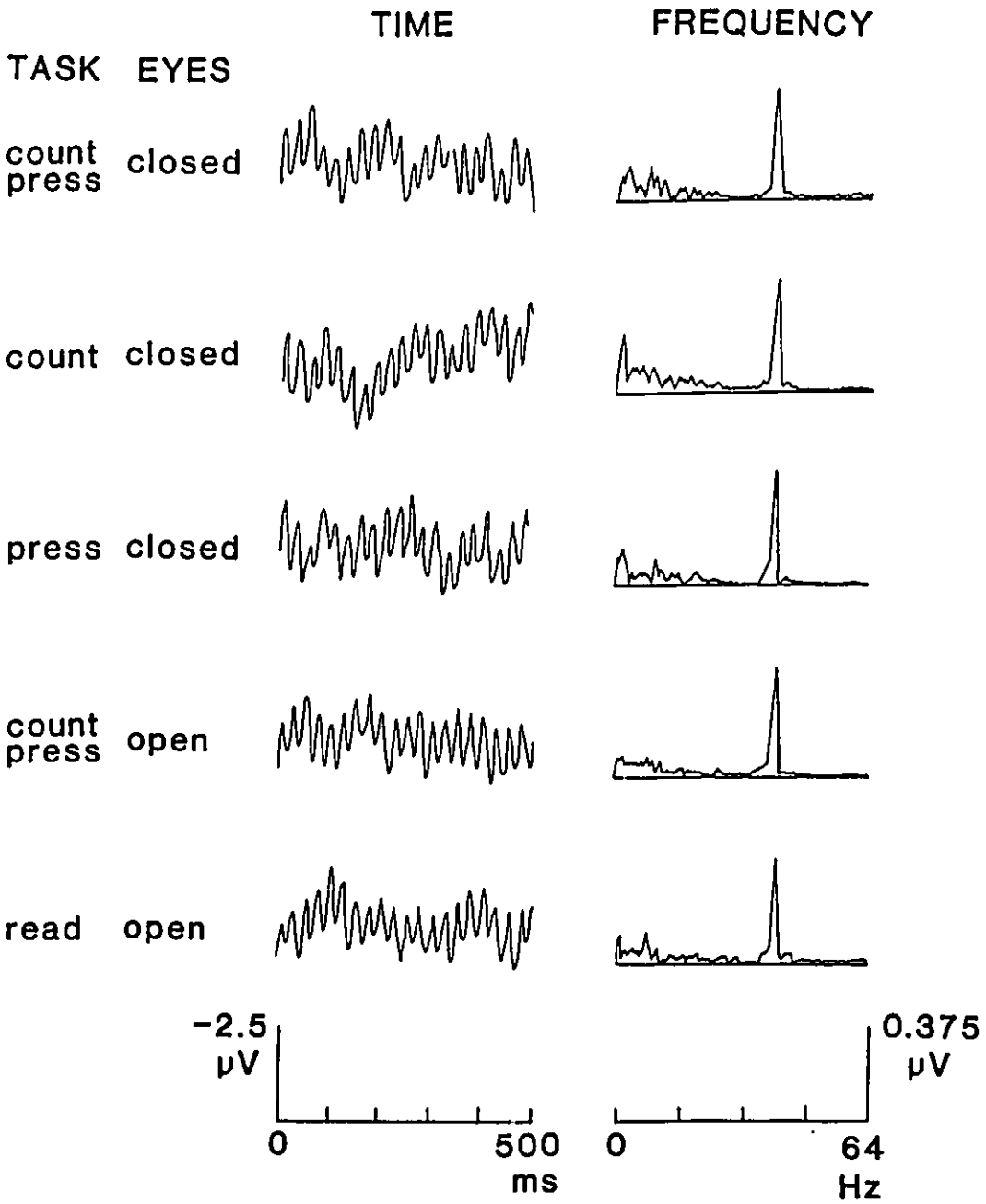
Measurements from Cz.

Condition			Time Domain	Frequency Domain	
Code	Eyes	Task	Amplitude (μV)	Amplitude (μV)	Phase (Cz)(degrees)
A	C	Press & count	0.49 (0.15)	0.48 (0.10)	48.2 (29.8)
B	C	Count only	0.48 (0.14)	0.46 (0.09)	48.6 (27.7)
C	C	Press only	0.49 (0.15)	0.48 (0.10)	49.0 (29.1)
D	O	Press & count	0.48 (0.14)	0.46 (0.09)	55.6 (29.0)
E	O	Ignore (Read)	0.44 (0.14)	0.43 (0.09)	58.0 (26.8)
		ANOVA	$P < 0.05$	$P < 0.05$	$P < 0.001$

Figure 1

Average unfiltered waveforms (left) recorded from Cz for the 10 control subjects and corresponding amplitude spectra (right) for each condition. Amplitude spectra obtained by fast Fourier transform. In the time-domain, negativity at the active electrode is plotted upward in this and all subsequent figures.

FIGURE 1


TIME
FREQUENCY
TASK
EYES
count press
closed
count
closed
press
closed
count press
open
read
open
-2.5 μV
0
500 ms
0.375 μV
0
64 Hz

40 Hz activity is reduced and not clearly distinguishable from background noise which is particularly high during these periods. Although there is some 40 Hz activity during surgery, it is not clearly distinguishable from the adjacent frequencies. The high-frequency peak during surgery is faster than 40 Hz and largely due to power line artifact (60 Hz).

The average measurements are presented in Table 2. Results of the ANOVAs yielded significant main effects for the period of recording for amplitude in both time-domain ($P < 0.001$) and frequency domain ($P < 0.001$). The ANOVA for phase yielded no significant main effect. There were no significant effects due to N_2O and no interactions.

Time-domain results showed a pronounced amplitude reduction during surgery compared with pre-induction, late induction and emergence ($P < 0.01$). No other comparisons approached significance.

Frequency-domain results also showed a profound amplitude reduction during surgery compared with pre-induction ($P < 0.01$). In contrast to time-domain measurements the amplitude was reduced by more than 50% during late induction ($P < 0.01$) compared with early induction. The amplitude during late induction and emergence were larger than during surgery. These differences nearly reached significance ($0.01 < P < 0.05$). There was a significant amplitude increase during recovery compared with emergence ($P < 0.01$). The amplitude during recovery was significantly smaller than during pre-induction ($P < 0.01$).

Data from individual subjects are shown in Fig. 3 to further examine the discrepancy between time-domain and frequency-domain results during late induction and emergence. With both methods, transition from early to late induction resulted in an amplitude decrease for all patients except one. For that patient, time-domain measurements showed

Table 2: AUDITORY STEADY-STATE RESPONSE - ANESTHETIZED PATIENTS

Mean and standard deviation (in brackets) for the anesthetized patients.

N = number of patients. Measurements from Cz.

Period	N	Time Domain Amplitude (μV)	Frequency Domain Amplitude (μV)	Frequency Domain Phase (degrees)
Pre-induction	10	0.42 (0.20)	0.41 (0.13)	57.2 (39.8)
Induction (early)	7	0.46 (0.20)	0.40 (0.12)	45.9 (41.0)
Induction (late)	7	0.32 (0.21)	0.17 (0.11)	5.2 (92.3)
Surgery	10	0.06 (0.02)	0.03 (0.01)	-12.3 (119.0)
Emergence	8	0.30 (0.23)	0.13 (0.09)	-15.7 (90.7)
Recovery	9	0.29 (0.11)	0.24 (0.07)	0.2 (43.0)
ANOVA (main effect)		P < 0.001	P < 0.001	NS

Figure 2

Average unfiltered waveforms (left) recorded from Cz for anesthetized patients and corresponding amplitude spectra (right) for each period. Amplitude spectra obtained by fast Fourier transform. Number of sweeps given in brackets below each period.

FIGURE 2

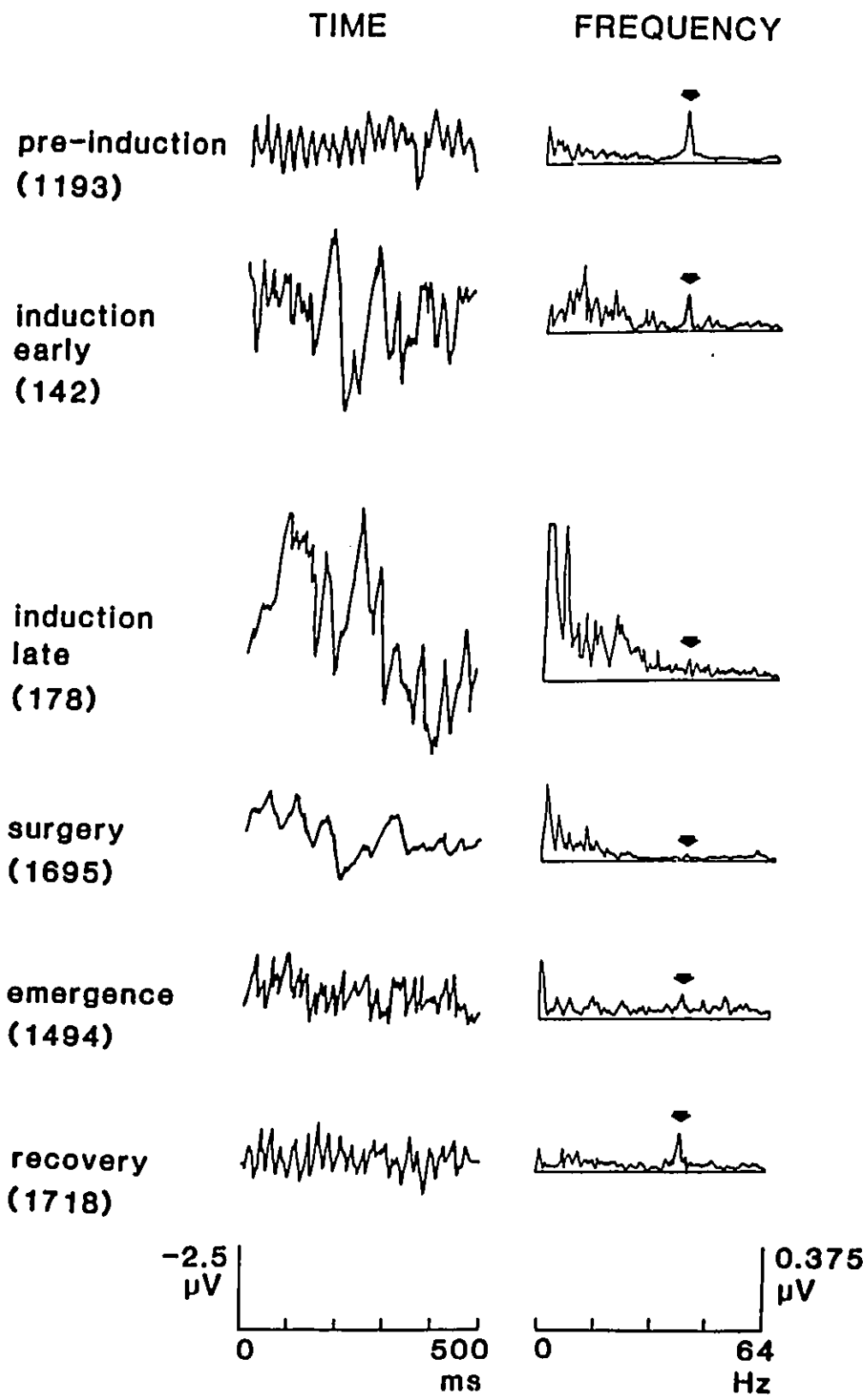
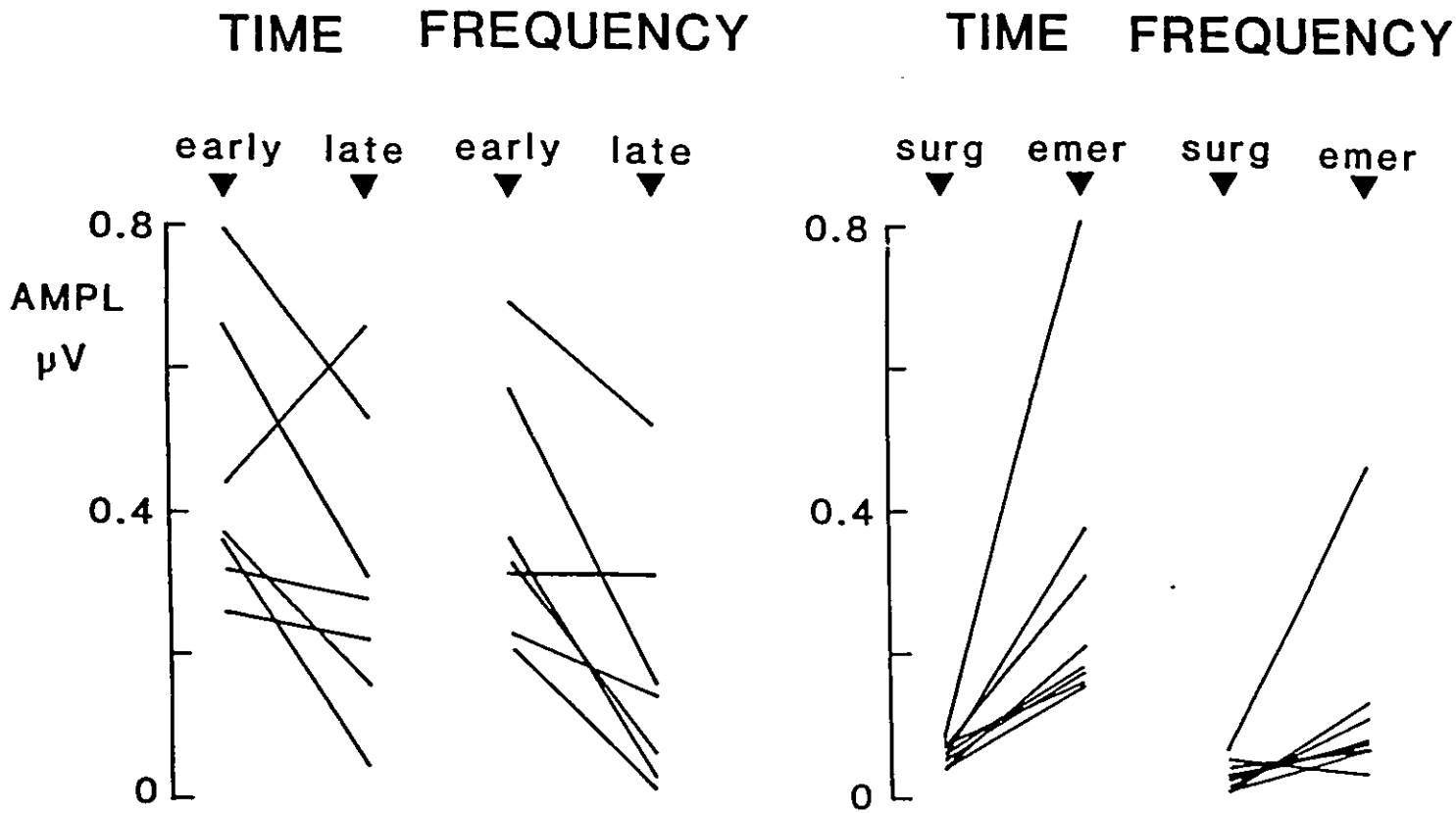

TIME
FREQUENCY
pre-induction
(1193)
induction
early
(142)
induction
late
(178)
surgery
(1695)
emergence
(1494)
recovery
(1718)
-2.5
μV
0
500
ms
0.375
μV
0
64
Hz

Figure 3

Amplitude changes for each subject from early to late induction and from surgery to emergence measured in time-domain and in the frequency-domain.

FIGURE 3


TIME FREQUENCY
TIME FREQUENCY
early
late
early
late
surg
emer
surg
emer
0.8
AMPL
μV
0.4
0
0.8
0.4
0

an amplitude increase and frequency-domain measurements showed no amplitude change. Transition from surgery to emergence was accompanied by increased amplitude with both methods except for one patient who showed a decreased amplitude only with frequency-domain measurements. The increase was, in general, more pronounced with time-domain measurements.

Correlation coefficients between frequency-domain and time-domain amplitude values were 0.99 ($P < 0.001$) during pre-induction; 0.97 ($P < 0.001$) during early induction; 0.82 ($P < 0.05$) during late induction; 0.35 ($P = 0.32$) during surgery; 0.89 ($P < 0.001$) during emergence; and 0.84 ($P < 0.01$) during recovery.

Phase-coherence and Hotelling's T^2 statistic indicated that the responses were consistent between subjects ($P < 0.01$) during pre-induction, early induction and during recovery. Borderline values ($0.05 < P < 0.10$) were obtained for late induction and emergence. No consistent response was present during surgery ($P = 0.2$).

Increasing stimulus intensity from 90 to 100 dB (peak SPL) during surgery in three patients augmented the amplitude of the ASSR from 0.04 to 0.08 μV (frequency-domain) and 0.05 to 0.08 μV (time-domain). There were no consistent phase changes.

In two patients in whom tracheal intubation was delayed for 3-4 minutes, the effects of thiopental alone were studied. The ASSR amplitude measured in the frequency-domain decreased to a level comparable to surgical recordings. The response was smaller than 0.06 μV and there was no recognizable 40 Hz peak in the spectrum. There was a fair amount of high-frequency activity in the recording. With time-domain measurements the amplitude also decreased but remained at about 0.10 μV i.e. twice the amplitude during surgery. In three patients of

the isoflurane-only group, the ASSR was recorded before emergence when the end-tidal concentration of isoflurane reached 0.5%. The amplitudes measured in the frequency-domain were 0.02, 0.03 and 0.03 μV. In the time-domain the values were 0.08, 0.06 and 0.07 μV. These are comparable to those obtained during surgery.

Brain-stem responses

Results are presented in Table 3 and Fig 4. The latency of wave I was increased during surgery by 0.07 ms. Waves III and V were delayed by 0.23 and 0.37 ms respectively. The amplitudes of waves I and III were slightly increased whereas the amplitude of wave V was decreased. The mean ASSR amplitude (measured in frequency domain) for these three patients was 0.44 μV pre-operatively and 0.05 during surgery. Similar values were obtained in the time-domain.

EEG

Results are presented in Table 4. ANOVAs were significant ($P < 0.001$) for EEG power, relative beta power, median and 95% quantile frequency. The ANOVA for the ratio (alpha + beta)/(delta + theta) was also significant ($P < 0.01$). There were no effects due to N_2O and no interactions.

Two-tailed paired t-tests were used because the direction of changes was not predictable. There was a significant increase in total EEG power after induction ($P < 0.01$ compared with pre-induction). EEG power returned toward baseline during surgery. Beta activity decreased

Table 3: AUDITORY BRAIN-STEM RESPONSES

Mean values for three patients. Right and left side collapsed.

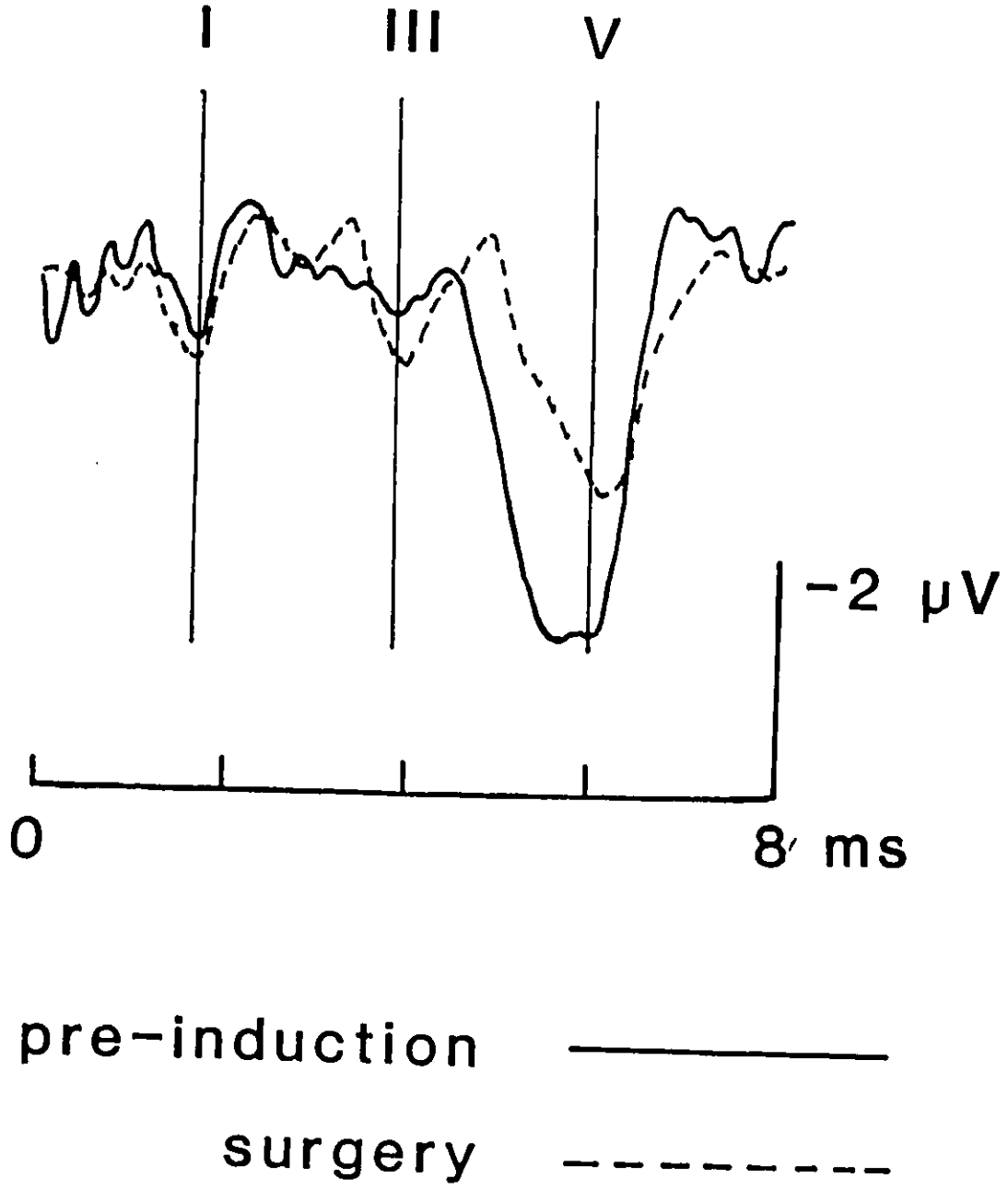
Measurements from Cz with reference to ipsilateral mastoid.

Wave	PRE-INDUCTION		SURGERY	
	Latency (ms)	Ampl (μV)	Latency (ms)	Ampl (μV)
I	1.85	0.15	1.92	0.20
III	3.97	0.15	4.20	0.22
V	6.01	0.51	6.38	0.33

Figure 4

Auditory brain-stem responses. Average waveforms for three patients during pre-induction and surgery. Right and left side collapsed. Filtered 50-2500 Hz.

FIGURE 4



significantly during surgery ($P < 0.01$ compared with pre-induction). It increased significantly during emergence ($P < 0.001$ compared with surgery). It remained high during recovery ($P < 0.01$ compared with pre-induction). The median frequency showed similar changes except that there was no difference between pre-induction and recovery. The ratio (alpha + beta)/(theta + delta) increased significantly ($P < 0.01$) from surgery to emergence. The 95% quantile frequency decreased after induction ($P < 0.01$) and remained at that same level during surgery. During emergence it increased ($P < 0.01$ compared with surgery) even above pre-induction values ($P < 0.01$). There was no change from emergence to recovery.

Unfiltered EEG segments (Cz) and power spectra from two representative patients are shown in Fig. 5. End-tidal concentrations of N_2O and isoflurane were 60% and 0.3% respectively for patient A (0.9 MAC). Patient B received only isoflurane in oxygen (1.0% end-tidal) (0.9 MAC). Alpha and delta activity predominated pre-operatively. During induction there was a large increase in EEG power particularly in the delta and theta bands. During surgery, delta activity predominated with some superimposed alpha activity. During emergence patient A showed a return towards the pre-operative pattern whereas patient B showed diffuse activity across the spectrum. During recovery both patients showed predominant delta and theta activity with low level activity across the spectrum. Muscle artifacts are evident in the EEG segments during emergence and recovery.

Table 4A: EEG - POWER AND QUANTILE FREQUENCIES

Mean and standard deviation (in brackets) for the anesthetized patients.

N = number of patients. Measurement from Cz.

Period	N	EEG power (μV^2)	median frequency (Hz)	95% quantile frequency (Hz)
Pre-induction	10	2.7 (5.6)	6.0 (3.5)	20.2 (6.1)
Induction	7	23.1 (14.7)	4.7 (3.9)	13.5 (6.0)
Surgery	10	4.8 (1.2)	3.9 (2.5)	13.4 (4.5)
Emergence	8	1.7 (0.7)	11.3 (4.6)	28.2 (1.4)
Recovery	9	0.7 (0.2)	8.1 (3.8)	27.8 (1.7)
ANOVA (main effect)		$P < 0.001$	$P < 0.001$	$P < 0.001$

Table 4B: EEG - RELATIVE POWER

Mean and standard deviation (in brackets) for the anesthetized patients.

Measurement from Cz.

Period	delta (0.5-3.4 Hz)	theta (3.5-7.4 Hz)	alpha (7.4-13.4 Hz)	beta (13.4-30 Hz)	(alpha + beta)/ (delta + theta)
Pre-induction	0.53 (0.23)	0.20 (0.14)	0.21 (0.14)	0.06 (0.04)	0.37 (0.26)
Induction	0.66 (0.17)	0.19 (0.10)	0.12 (0.13)	0.03 (0.04)	0.23 (0.27)
Surgery	0.64 (0.15)	0.18 (0.05)	0.16 (0.12)	0.02 (0.02)	0.26 (0.23)
Emergence	0.42 (0.13)	0.19 (0.07)	0.23 (0.08)	0.16 (0.09)	0.72 (0.38)
Recovery	0.54 (0.21)	0.15 (0.07)	0.20 (0.13)	0.11 (0.04)	0.54 (0.37)
ANOVA (main effect)	NS	NS	NS	$P < 0.001$	$P < 0.01$

Figure 5, A and B

Electroencephalogram recorded from Cz for two representative patients. One patient (A) received N_2O (60% end-tidal) and isoflurane (0.3% end-tidal). The other patient (B) received only isoflurane (1% end-tidal). Pre-induction alpha activity denoted by the arrows. Low frequency power has been clipped during induction for both patients and during surgery for patient B.

FIGURE 5A

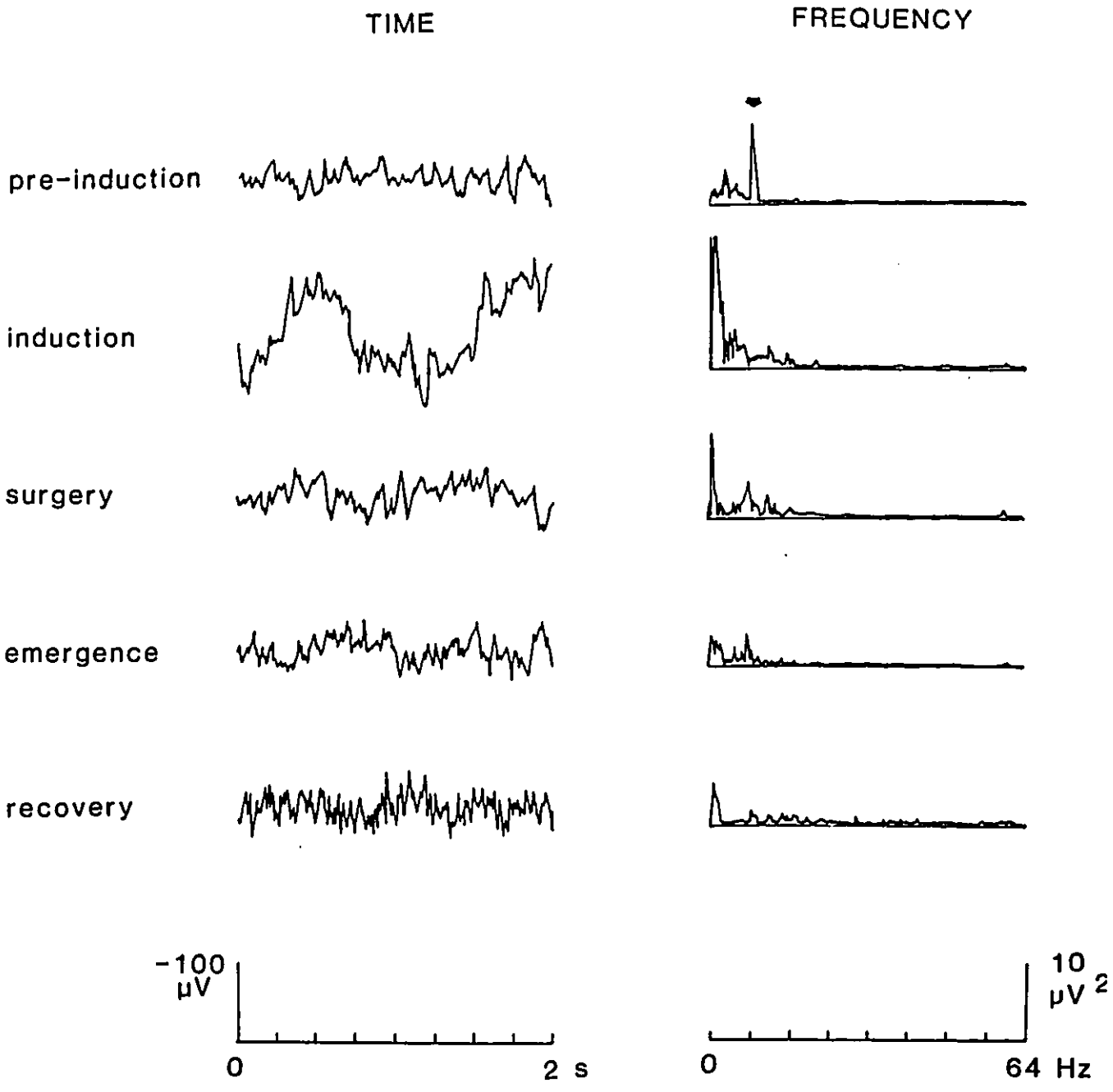
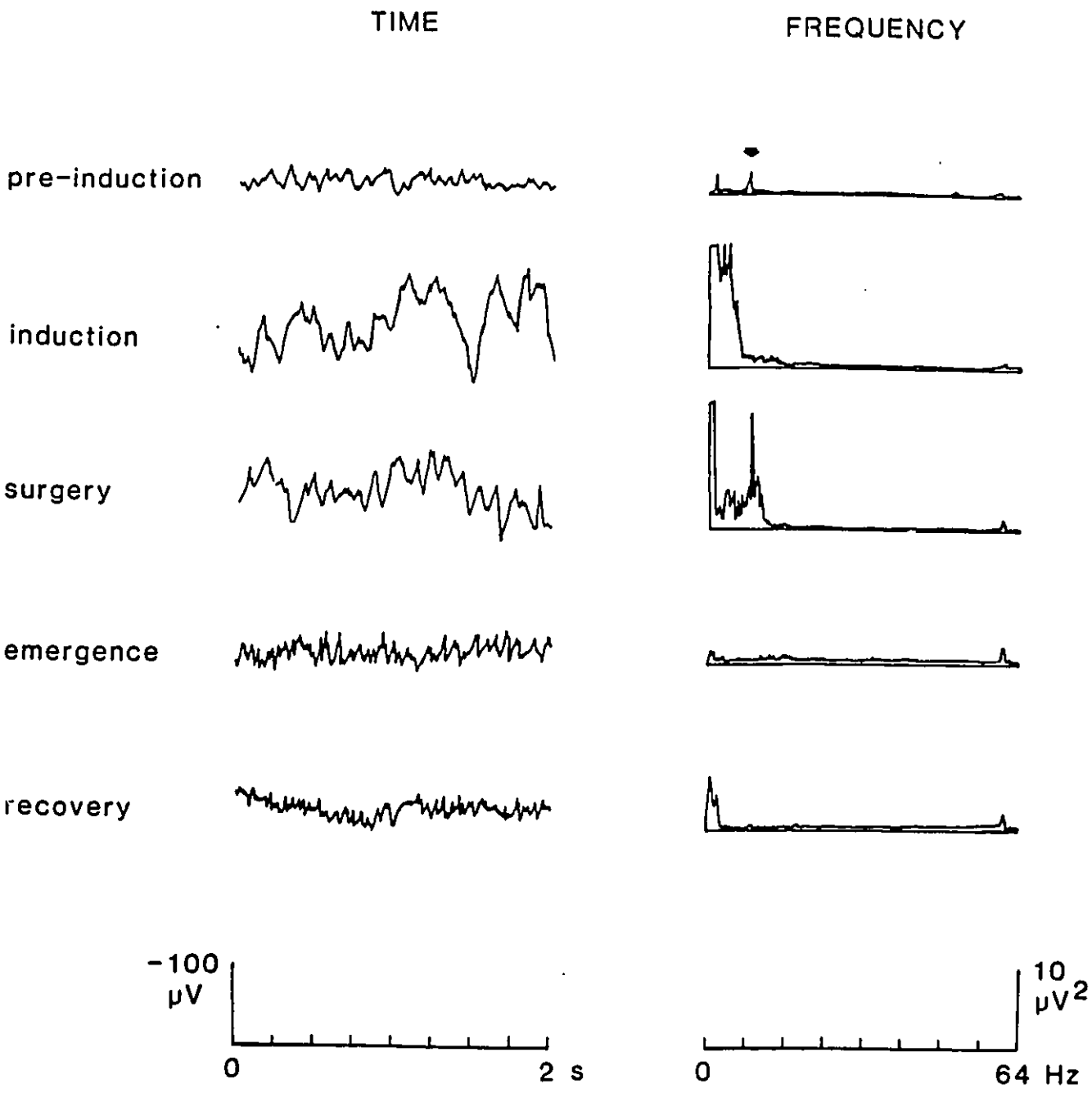

TIME
FREQUENCY
pre-induction
induction
surgery
emergence
recovery
-100 μV
0
2 s
10 μV 2
0
64 Hz

FIGURE 5B


TIME
FREQUENCY
pre-induction
induction
surgery
emergence
recovery
-100 μV
0
2 s
10 μV²
0
64 Hz

D I S C U S S I O N

Awake Controls

The ASSR recordings were satisfactory and comparable to those previously recorded (Linden et al., 1987). The responses were consistent between subjects. The amplitude of the ASSR was similar for all ATTEND conditions (i.e. A to D) for both time-domain and frequency-domain measurements.

There were two unanticipated findings. First, the amplitude was slightly but significantly reduced in the IGNORE condition. This was unexpected in view of the reported absence of attentional effects on the ASSR (Linden et al., 1987). The subjects may possibly have become drowsy during the IGNORE condition because they were bored by the reading material. Decreased level of arousal is known to reduce the amplitude of the ASSR (Galambos and Makeig, 1988). Alternatively, it is also possible that the amplitude of the ASSR is slightly increased during attention. Several factors may explain the discrepancy between this study and the study of Linden et al. (1987). The present study used more observations, a higher stimulus-intensity and a simpler detection-task. Second, the phase of the ASSR with eyes open was slightly less than in the eyes-closed condition. We are not aware that anyone else has seen this and we are at a loss to explain it.

Anesthetized Patients

Steady-state response

This study demonstrates that the amplitude of the 40 Hz auditory steady-state response (ASSR) is reduced to 5-15% of control values

during anesthesia and surgery with isoflurane (0.9 MAC) or isoflurane/N_2O (1.2 MAC). The response was undistinguishable from noise during surgical anesthesia. The findings replicate the observations by Hogan (1987) who described a 78% amplitude (time-domain) reduction during isoflurane/N_2O (1.2 MAC) anesthesia. At comparable MAC levels, Heneghan et al. (1987) described about a 50% reduction of the amplitude of the transient auditory middle latency evoked response during anesthesia with isoflurane and N_2O. Most anesthetic agents increase the latency and reduce the amplitude of the transient middle latency auditory response (Jones, 1987; Madler and Pöppel, 1987). This will interfere with the formation of the ASSR which depends in part on the overlapping of the response to successive stimuli. The ASSR is therefore probably more susceptible to anesthesia than the transient response.

Measures of phase coherence and Hotelling's T^2 statistic confirmed that the responses were consistent between subjects ($P < 0.01$) during pre-induction, early induction and during recovery but not during surgery. During late induction and emergence the P value was borderline ($0.05 < P < 0.10$). A small 40 Hz peak is present during these periods but it does not stand out relative to the increased activity in the adjacent frequencies (Fig. 2).

The attenuation cannot be accounted for by conductive hearing loss because the auditory brain-stem response, recorded in three patients, showed no evidence of a substantial increase in wave I latency. Conductive hearing loss is virtually always associated with increased wave I latency (Chiappa, 1985). The 0.07 ms prolongation of wave I latency would correspond to only 2 dB attenuation of stimulus intensity (Chiappa, 1985). The latencies of waves III and V were slightly

prolonged, as expected during isoflurane anesthesia (Manninen et al., 1985). The auditory brain-stem response was recorded in only three patients because of time constraints. We feel that these results nevertheless provide adequate evidence that anesthesia markedly reduces the ASSR without affecting wave I of the brain-stem response and that consequently, the ASSR reduction is not due to conductive hearing loss. Manninen et al. (1985) reported that at 1% end-tidal isoflurane the latency increase was 0.28 ms for wave III and 0.60 ms for wave V. We observed similar changes at these levels of isoflurane, the increase in the latencies of waves III and V being 0.23 ms and 0.37 ms respectively. Manninen et al. (1985) did not describe their amplitude measurements but their Fig. 1 (one subject) shows a 20-30% amplitude reduction for wave V and no change in wave I during 1% end-tidal isoflurane. We observed similar changes. Heneghan et al. (1987) described an increase in the latency of waves III and V with isoflurane (0.6 - 2.9%) and 70% N_2O but found no amplitude changes. Fentanyl did not alter the brain-stem responses in doses up 50 $\mu g. kg^{-1}$ (Samra et al., 1984).

Increasing the intensity of the stimuli by 10 dB during surgery increased the amplitude of the ASSR although the response remained well below awake levels. This suggests that the response may still be present during anesthesia despite being markedly reduced in amplitude.

On the basis of frequency-based measurements it appears that the ASSR became attenuated during late induction. The injection of thiopental was completed at that time and no other drug had been given except vecuronium. Therefore thiopental alone can attenuate the ASSR. In two patients the effect of thiopental alone could be studied longer because tracheal intubation was delayed. The ASSR amplitude measured in the frequency-domain dropped to values comparable to those during

surgery 30-90 minutes later. Because of rapid redistribution, the residual effects of thiopental during surgery may be assumed to be negligible. Thus the change seen with thiopental or isoflurane is similar, suggesting that the change is not agent-specific.

Furthermore the attenuation of the ASSR does not appear to be dose-dependent. Recordings in three patients at 0.5% end-tidal isoflurane were similar to those obtained during surgery (1.0% end-tidal isoflurane). This contrasts with the dose-dependent effects of isoflurane on the transient auditory middle latency response (Heneghan et al., 1987). The amplitude of the ASSR appears to be related to the level of arousal.

There was a discrepancy between time-domain and frequency-domain measurements for the amplitude of the ASSR during late induction. Time-domain measurements showed that the response remains above 75% of pre-op values whereas frequency-domain measurements yielded values of 41% of baseline. The discrepancy can be traced to the band-pass difference between methods. The band-pass for time-domain measurements was wider (38-42 Hz) than the single frequency band pass of the fast Fourier transform. Measurements of the "40 Hz response" in the time-domain can therefore be contaminated by activity in the surrounding frequencies. Muscle artifacts are the most likely cause of contamination. The fast activity associated with the early effects of thiopental is a less likely source of contamination because that activity rarely exceeds 30 Hz (Clark and Rosner, 1973; Stockard and Bickford, 1981). The fast activity is followed by 5-12 Hz waves and later by large 1-3 Hz polymorphic waves. There is no fast activity in our EEG tracings for induction (Fig. 5) because they show the late effects of thiopental.

A discrepancy between time- and frequency-domain methods also occurred during emergence. Time-domain measurements showed that the response returns to above 70% of pre-operative values whereas frequency-domain measurements yielded values of 30-40% of baseline. Muscle artifacts, evident on the unprocessed EEG, provide the most likely explanation.

During recovery both methods yielded comparable ASSR amplitude (60% of pre-operative baseline in the frequency-domain and 70% in the time-domain).

Should the ASSR be measured in time- or frequency-domain? Frequency-domain measurements probably reflect more accurately the amplitude of the ASSR, particularly when the signal is contaminated by activity near 40 Hz. The effects of noise in these adjacent frequencies could be further reduced in the frequency-domain by increasing the time of recording and by thus decreasing the bandwidth of the points in the fast Fourier transform (REGAN 1989). The amplitude of the ASSR measured in the frequency-domain followed more closely the level of arousal as assessed by the responsiveness to the environment. The ASSR amplitude (frequency-domain) and responsiveness to the environment were both maximal pre-operatively, decreased during induction, were minimal during surgery and progressively returned toward pre-operative levels during emergence and recovery. By contrast, with time-domain measurements surgical recordings were clearly demarcated from all others. The clear transition from surgery to emergence is interesting but must be interpreted with caution because of the contamination by increased muscle activity. In a paralyzed patient, it might not be as noticeable.

Despite the discrepancy between time-domain and frequency-domain methods there was a high and significant correlation between the two

measures for all periods except surgery. The lack of correlation during surgery is due to the absence of any clear response.

EEG

The increased EEG power after induction is consistent with the known effects of thiopental (Clark and Rosner, 1973; Stockard and Bickford, 1981). Of all the EEG parameters, it is the 95% quantile frequency which showed the most appropriate changes with the various stages of anesthesia. There was a significant decrease after induction which persisted during surgery. The 95% quantile frequency reached values above control during emergence and recovery. In all likelihood contamination by muscle artifacts partly accounts for this increase of the 95% quantile frequency during emergence and recovery. There is overlap between the power spectrum of the EEG and of the muscle activity (Bickford, 1979). Muscle artifacts may also account for the increase of the median frequency and of the activity in the beta band from surgery to emergence. Muscle artifacts complicate interpretation of the EEG and may easily invalidate procedures which attempt to summarize EEG data as a single number. The importance of muscle artifacts is frequently overlooked because many EEG and evoked potentials studies focus primarily on pre-anesthetic, post-induction and surgical stages. Since emergence from anesthesia is frequently associated with increased muscle activity (e.g. shivering, limb movements) complete elimination of muscle artifacts is difficult. Of the observed EEG changes from surgery to emergence those due to muscle artifacts would not occur in paralyzed patients. It is therefore difficult to predict the EEG changes in fully paralyzed patients emerging from anesthesia.

Conclusion

We conclude that the ASSR constitutes a promising tool for assessing the level of anesthesia. The amplitude of the ASSR is preferably measured in the frequency-domain. The amplitude of the ASSR appears to vary with the level of arousal. Its attenuation by general anesthetics does not appear to be agent-specific or dose-dependent. It is less influenced by muscle artifacts than the EEG.

E X P E R I M E N T 2

M E T H O D S

Subjects

The project was approved by the Institutional Research Ethics Committee. Written informed consent was obtained from all subjects. The normal unanesthetized subjects from Experiment 1 also participated in this study. They were tested in a sound-attenuated, electrically shielded room. Fourteen elective surgical patients (8 females) were tested. The mean age was 36 years (range: 21-61). All patients were free of neurological or otological disease. Ten of these patients participated in Experiment 1. Surgical procedures consisted of: plastic surgery (8 patients), orthopedic surgery (4 patients), urological surgery (2 patients), general surgery (1 patient), and thoracic surgery (1 patient).

Anesthetic Technique

The anesthetic technique was similar to that described in Experiment 1. Anesthesia was maintained with fentanyl (3 $\mu g.kg^{-1}$) and isoflurane (0.5-1.5% end-tidal) in O_2 (seven patients) or in N_2O (60% end-tidal) in O_2 (seven patients).

Stimuli

The transient late auditory EPs were produced by 700 Hz tones already described in Experiment 1.

Recording

The EEG was recorded in a manner similar to that described for the ASSR (Experiment 1). Recordings for Experiment 1 and the present Experiment were done concurrently. A fifth channel was used to monitor button presses up to 1480 ms after stimulus. Duration of the analog-to-digital (AD) sweep was 1490 ms. Sampling frequency was 688 Hz per channel. The interval between onset of AD sweeps was 2000 ms. There was only one target stimulus per AD sweep. It always started 10 ms after onset of sweep. The probability that a target stimulus would occur during an AD sweep was 0.33. The average interval between target stimuli was therefore six s. Sweeps were averaged separately for hits (detected targets i.e. button press present) and misses (missed target i.e. button press absent). Sweeps contaminated by excessive muscle or eye movements were rejected. The rejection level for controls was $\pm$ 87.5 μV for all channels. For the anesthetized patients the level was $\pm$ 175 μV. Less stringent rejection criteria were used with the anesthetized patients because EEG changes due to the anesthetic agents would have caused excessive rejection. A recording block consisted of 45 AD sweeps (duration 90 s) for controls and of 100 AD sweeps (200 s) for surgical patients.

Design

We initially tested awake control subjects to ascertain that adequate responses could be obtained with the experimental paradigm. Recordings were obtained in the same five conditions described for the ASSR (Experiment 1). There were two recording blocks for each condition. The order of conditions and replications was counterbalanced within and

across subjects. Recordings for each condition were averaged prior to measurement.

With anesthetized patients recordings were obtained during the following periods: pre-induction, induction, surgery, emergence and recovery. Patients kept their eyes closed and were instructed to press a button following each target whenever possible (similar to condition C above). The injection of thiopental began 15 - 30 sec after the beginning of the induction recording and lasted one minute. Recordings during surgery were done at stable (10 min. period) levels of isoflurane: 0.5% end-tidal when administered with 60% N_2O and 1.15% end-tidal when administered in oxygen alone. After surgery, the trachea was extubated as soon as the patient was able to obey simple commands. Emergence was defined as the 10 min. period immediately following tracheal extubation. Within each period other than induction multiple recordings were usually carried out. All individual recordings from each period for each patient were combined separately for hits and misses prior to measurement. Recordings could not be obtained from all patients for all periods because of patient-related factors like movements or shivering.

Analysis

Awake Controls

The average waveforms were digitally filtered (0-30 Hz) prior to analysis. N1 was measured at Cz and defined as the most negative peak occurring 80-180 ms after stimulus and before P2. (P2 was defined as the maximum positivity occurring 120-250 ms after the stimulus - it was used to help identify N1 but was not included in data analysis.) P3 was defined as the most positive peak occurring 250-450 ms after stimulus.

It was measured at both Fz and Pz. Amplitude was measured relative to baseline (initial 10 ms of sweep). To evaluate the scalp distribution of N1 and P3, the amplitudes at Fz, Cz and Pz were measured at the peak latency of N1 at Cz and P3 at Pz.

The amplitude and latency measurements were submitted to one-way ANOVAs for repeated measures to assess the effects of the experimental conditions. Scalp-distribution data were submitted to a 3 (electrode location) X 5 (condition) ANOVA for repeated measures on both levels. Similarly a 2 (electrode location) X 5 (condition) ANOVA for repeated measures on both levels was used to compare the P3 latency at Fz and Pz. The Geisser-Greenhouse adjustment of the level of significance was used for all repeated measures ANOVAs (Kirk, 1982; Dixon, 1985). Tukey's HSD test (KIRK 1982) was used for post-hoc comparisons.

Anesthetized Patients

The combined waveforms were digitally filtered (0-10 Hz) prior to analysis. A narrower bandpass was used because the data were noisier than those from awake controls. Measurements based on averages of less than six sweeps were excluded because of excessive variability. Average amplitudes over a latency range were used instead of peak measurements because many recordings did not reveal clearly recognizable waves. The amplitude of N1 was defined as the average amplitude at Cz from 100 to 200 ms after the stimulus. The amplitude of the P3 was the average amplitude from 300 to 400 ms after the stimulus. It was measured at Fz and Pz.

The amplitude measurements were first examined with T-tests to determine if there were any differences between patients having received isoflurane in O_2 and those having received isoflurane in N_2O/O_2. There were no significant differences ($P > 0.2$). The results from the two

groups were therefore pooled. The pooled measurements were submitted to one-sample t-tests to determine whether a wave was present i.e. whether the mean amplitudes were significantly different from zero. Paired one-tailed t-tests were then used to compare the amplitude for hits and misses during induction and recovery. (During pre-induction, surgery and emergence the number of observations for either hits or misses was insufficient for testing.) Paired one-tailed t-tests were also used to compare the amplitude for hits during pre-induction with that of hits during induction and recovery. (The number of hits during emergence was too small for testing.) T-tests were used instead of analysis of variance for repeated measures because data could not be obtained from all patients for all periods. Scalp distribution data were analyzed with one-way ANOVAs for repeated measures with Geisser-Greenhouse adjustment. With both awake control subjects and anesthetized patients, the criterion for significance was set at $P < 0.05$ for the ANOVAs and at $P < 0.01$ for all other tests.

R E S U L T S

Awake controls

Measurements from individual subjects are summarized in Table 5 and 6. The average waveforms for the 10 subjects is shown in Fig. 6. The P3 amplitude (Table 5) was significantly ($P < 0.001$) smaller for the IGNORE condition (E) compared with the ATTEND conditions (A - D) both at Fz and Pz. In the IGNORE condition the P3 amplitude at Fz was slightly larger than at Pz but the difference was not significant. There was no other significant amplitude differences, the amplitude of N1 being approximately the same under all recording conditions.

There were no significant main effects for latency (Table 6). The average latency for N1 was 137 ms. The mean P3 latency was 315 ms at Fz and 327 ms at Pz (ANOVA, $P < 0.05$). There were no interactions.

The scalp distribution (Table 7) revealed that the N1 was largest at Cz in all conditions. This difference was significant (ANOVA, $P < 0.01$) and the amplitude at Cz was significantly larger than at either Fz or Pz (Tukey's HSD, $P < 0.01$). There were no significant interactions. For the P3, the usual relation ($Fz < Cz \leq Pz$) was present for all conditions except D but the differences were not significant.

Anesthetized Patients

Anesthetic Management

The average interval between start of induction and extubation was 134 min (SD 69). Recording in the recovery room was started on average 41 min (SD 26; range 10-79) after extubation and was completed 66 min (SD 32; range 23-114) after extubation.

Table 5: LATE AUDITORY EVOKED POTENTIALS - AWAKE CONTROL SUBJECTS - AMPLITUDE

Mean amplitude (μV) and standard deviation (brackets) for 10 subjects.

condition			measurements		
Code	Eyes	Task	N1 (Cz)	P3* (Fz)	P3* (Pz)
A	Closed	Press & count	-7.1 (5.4)	7.1 (2.3)	7.3 (2.0)
B	Closed	Count only	-6.5 (5.9)	6.7 (2.9)	6.7 (2.4)
C	Closed	Press only	-8.4 (2.8)	6.0 (3.5)	6.0 (2.9)
D	Opened	Press & count	-6.9 (4.3)	6.4 (4.2)	6.7 (3.0)
E	Opened	Ignore (read)	-6.1 (3.8)	4.3 (1.9)	3.3 (1.4)

*: Significant planned comparison E vs (A,B,C,D), $P < 0.001$

Table 6: LATE AUDITORY EVOKED POTENTIALS - AWAKE CONTROL SUBJECTS - LATENCY

Mean latency (ms) and standard deviation (brackets) for ten subjects.

condition			measurements			
Code	Eyes	Task	N1 (Cz)	P3* (Fz)	P3 (Pz)	Modal Reaction Time
A	Closed	Press & Count	142(20)	313(35)	322(24)	265(59)
B	Closed	Count only	144(27)	308(32)	324(25)	–
C	Closed	Press only	140(21)	325(20)	331(19)	278(54)
D	Open	Press & count	131(18)	320(24)	319(21)	273(67)
E	Open	Ignore (read)	128(16)	310(56)	340(60)	–
Mean across conditions			137	315	327	272

*: Significantly less than at Pz across conditions (2 x 5 ANOVA, $P < 0.05$)

Figure 6

This figure represents the grand mean responses from ten control subjects during five different conditions. The amplitude of the P3 in the ATTEND conditions (i.e. press and/or count) is larger (arrows) than in the READ (IGNORE) condition where the P3 is very small. Recordings from mid-frontal (Fz), vertex (Cz) and mid-parietal (Pz) electrodes. Right mastoid was the reference for all channels.

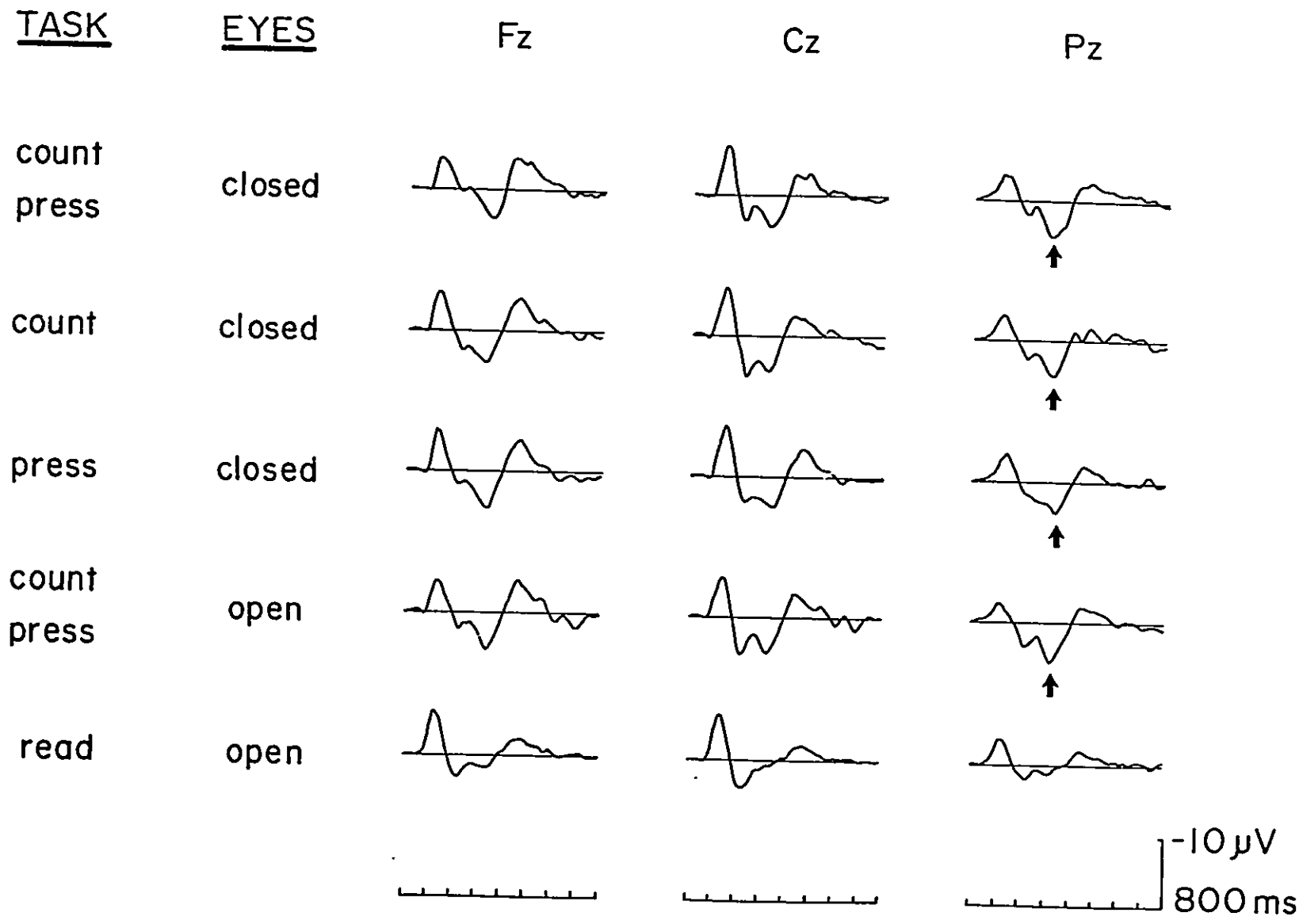

TASK
EYES
Fz
Cz
Pz
count press
closed
count
closed
press
closed
count press
open
read
open
-10 μV
800 ms

FIGURE 6

Table 7: LATE AUDITORY EVOKED POTENTIALS - AWAKE CONTROL SUBJECTS - SCALP DISTRIBUTION

Mean amplitude (μV) at each electrode location.

condition			N1			P3		
Code	Eyes	Task	Fz	Cz*	Pz	Fz	Cz	Pz
A	Closed	Press & Count	-4.2	-7.1	-3.8	4.1	5.1	5.9
B	Closed	Count only	-5.8	-6.5	-3.6	5.1	5.9	6.7
C	Closed	Press only	-5.6	-8.4	-4.0	5.5	5.1	6.0
D	Opened	Press & Count	-4.6	-6.9	-3.1	6.1	7.1	6.7
E	Opened	Ignore (Read)	-5.9	-6.1	-3.4	2.3	3.3	3.3
Mean across conditions			-5.3	-7.0	-3.5	4.6	5.3	6.0

*: Significant 5 x 3 ANOVA ($P < 0.01$); Cz absolute amplitude larger than at Fz and Pz (Tukey's HSD, $P < 0.01$).

The mean nasopharyngeal temperature during surgery was 36.1°C (SD 0.46; range 35.4-37.0). The mean end-tidal partial pressure of CO_2 during surgery was 27.8 mmHg (SD 2.0; range 27-33). For patients receiving isoflurane in N_2O the mean end-tidal concentrations were respectively 0.55% (SD 0.11) and 62% (SD 8) (1.1 MAC). For patients receiving isoflurane in oxygen, the mean end-tidal concentration was 0.96% (SD 0.08) (0.8 MAC). Fluctuations of the level of consciousness with time were similar to those described in Experiment 1.

Evoked Potentials

Measurements from individual patients are summarized in Table 8. The number of observations varies because data could not be obtained from all patients for all periods either because patients could not be tested (movements, shivering) or because the averages had less than six sweeps and were not measured. There were no effects due to N_2O (t-tests, $P > 0.2$) and the results from patients of both groups were therefore combined.

The average waveforms for the 14 patients are shown in Fig. 7. N1 is visible (downward arrows) for hits during pre-induction, induction and recovery. There also seems to be a small N1 for misses during recovery. A P3 is present at Fz and Pz (upward arrows) for hits during pre-induction, induction and recovery. For misses during recovery there are positive deflections in the P3 latency range at Fz and Pz but they are too small for definitive interpretation. There were no recognizable waves for hits during emergence as well as for misses during induction, surgery and emergence.

To determine the presence or absence of individual waves t-tests (one-tailed) were used to find if the mean amplitudes were different from zero. The amplitudes of N1 and of P3 at both Fz and Pz were

Table 8: LATE AUDITORY EVOKED POTENTIALS - ANESTHETIZED PATIENTS - AMPLITUDE

Mean and standard deviation (brackets) for 14 patients.

N is number of subjects.

Data could not be obtained from all patients for all periods.

Period/Type	N	Mean Amplitude (μV) N1 (100-200 ms) Cz	P3 (300-400 ms) Fz	Pz	Modal Reaction Time (ms)
Pre-induction Hits	(14)	-4.7 (4.0)*	3.4 (2.9)*	4.0 (2.8)*	252 (64)
Induction Hits	(9)	-3.2 (3.0)*	2.9 (2.1)*	2.7 (1.6)*	322 (93)
Induction Misses	(12)	1.7 (7.1)	1.4 (5.2)	0.2 (4.5)	—
Surgery Misses	(13)	-0.6 (3.1)	-0.5 (2.7)	0.2 (2.0)	—
Emergence Hits	(4)	-0.8 (3.0)	0.1 (2.5)	-0.6 (2.4)	639 (174)
Emergence Misses	(10)	-0.4 (1.8)	-0.0 (1.3)	0.2 (1.1)	—
Recovery Hits	(12)	-2.5 (2.5)*	2.7 (2.8)*	2.9 (1.9)*	354 (124)
Recovery Misses	(7)	-0.9 (1.2)	1.2 (1.2)	0.8 (1.2)	—

*: Different from zero (one-tailed t-test, $P < 0.01$)

Figure 7

This figure represents the grand mean responses from 14 patients pooled for each period and type of response. N is number of sweeps in each waveform. Downward arrows point to recognizable N1 waves on Cz. Upward arrows point to recognizable P3 waves at Pz. The number of misses during pre-induction was insufficient to obtain adequate waveforms. There were no hits during surgery.

FIGURE 7

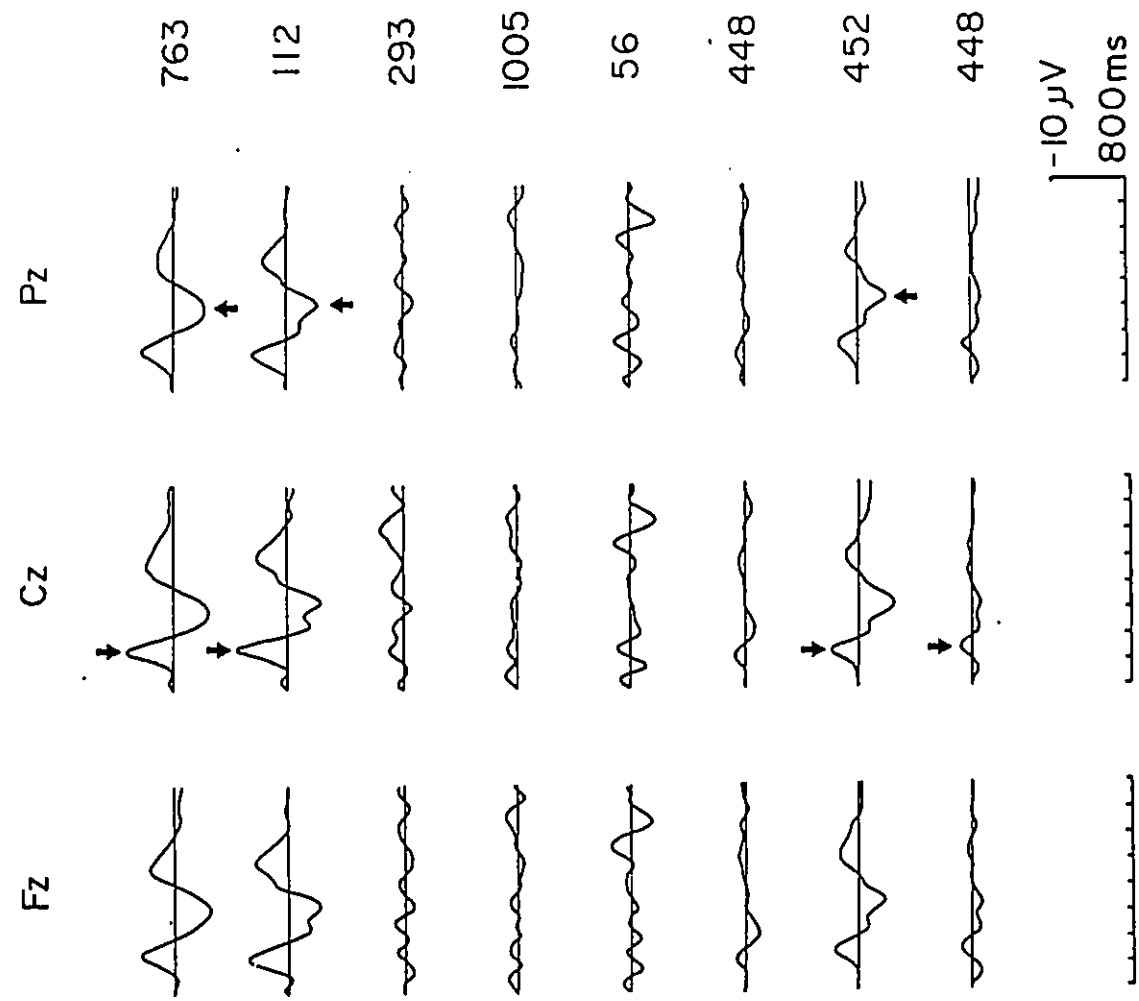

Fz
Cz
Pz
pre-induction
hits
763
hits
112
induction
misses
293
surgery
misses
1005
hits
56
emergence
misses
448
hits
452
recovery
misses
448
-10 μV
800ms

Table 9: LATE AUDITORY EVOKED POTENTIALS - ANESTHETIZED PATIENTS - SCALP DISTRIBUTION

Mean amplitude (μV) at each electrode location.

Periods with no clearly recognizable responses excluded.

	N1			P3		
Period/type	**Fz**	**Cz**	**Pz**	**Fz**	**Cz**	**Pz**
Pre-induction Hits	-3.7	-4.7*	-3.0	3.3	4.0	4.0
Induction Hits	-2.8	-3.2	-2.2	2.9	3.1	2.7
Recovery Hits	-2.1	-5.1	-1.9	2.7	3.2	2.9

*: Significantly larger than Pz amplitude (Tukey's HSD, $P < 0.01$).

significantly ($P < 0.01$) different from zero for hits during pre-induction, induction and recovery. For misses during recovery the amplitude of N1 and P3 nearly reached significance ($0.01 < P < 0.05$). The t-tests for misses during induction, surgery amd emergence as well as for hits during emergence were not significant.

The amplitudes of N1 at Cz and P3 at Fz and Pz for hits were larger than for misses of the same period during induction and recovery. However the difference was significant ($P < 0.01$) only for P3 at Fz and Pz and only during recovery. For pre-induction, surgery and emergence the number of either hits or misses was insufficient for similar comparisons.

The amplitude of all three waves for hits was larger during pre-induction than during induction but the differences were not significant. The amplitude for hits was significantly larger ($P < 0.01$) during pre-induction than during recovery for N1 and P3 at Pz but not for P3 at Fz.

The scalp distribution (Table 9) showed that the amplitude of N1 was maximal at Cz for hits during pre-induction, induction and recovery. The electrode differences reached significance only for pre-induction data (ANOVA, $P < 0.05$) where post-hoc testing revealed that N1 was larger at Cz than at Pz (Tukey's HSD, $P < 0.01$). The P3 amplitude was maximal at Cz and Pz during pre-induction. During induction and recovery the P3 amplitude was maximal at Cz. None of the P3 scalp distribution differences reached significance.

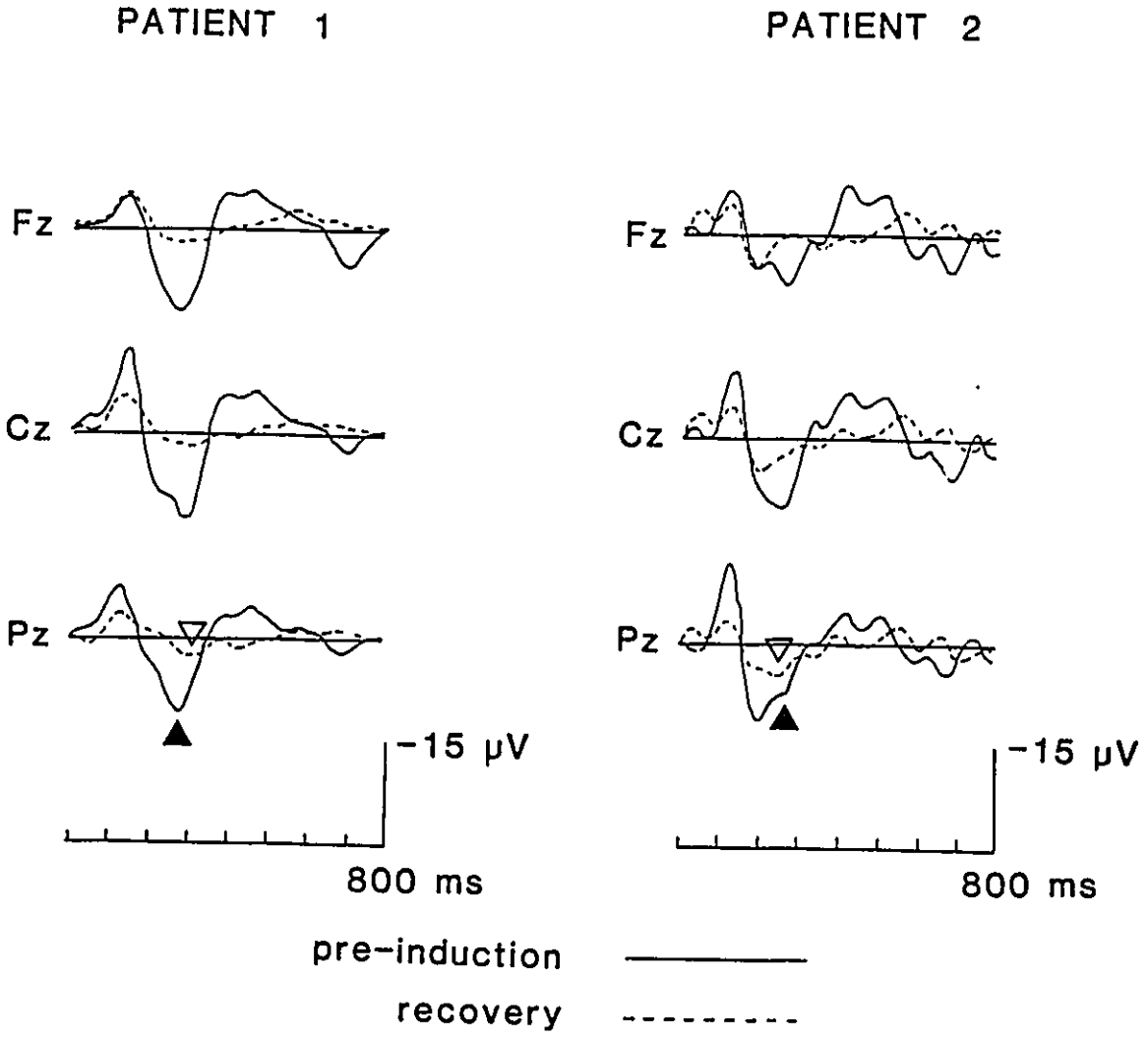
The time course of recovery of the EPs could not be examined in detail because of the 41 min. mean interval between extubation and recovery recordings. For two patients, however, testing in the recovery room occurred from 10 to 23 min. after extubation of the trachea. In

these patients the early signs of awakening (movements) preceded extubation by 2-3 min. The N1 and P3 waves are clearly recognizable during recovery (Fig 8).

Figure 8

Recording from two patients during pre-induction (solid line) and recovery (dashed line). Recovery recordings were started 10 min after extubation and lasted 13 min. The N1 and P3 during recovery are smaller than during pre-induction but are clearly recognizable. The filled triangles indicate the P3 during pre-induction; the empty triangles the P3 during recovery.

FIGURE 8


PATIENT 1
PATIENT 2
Fz
Cz
Pz
Fz
Cz
Pz
-15 μV
800 ms
-15 μV
800 ms
pre-induction
recovery

D I S C U S S I O N

Awake Subjects

The recordings were satisfactory and confirmed our expectations that the N1 amplitude would be the same for ATTEND and IGNORE conditions whereas the amplitude of the P3 would be much larger for the ATTEND conditions. The scalp-distribution of N1 followed the expected pattern of maximal negativity of Cz (Näätänen and Picton, 1987; Picton and Hillyard, 1988). The scalp-distribution of P3 was also anticipated ($Fz < Cz \leq Pz$) (Picton and Hillyard, 1988).

The amplitude and latency of N1 were not significantly affected by the recording conditions. This provides further evidence that simple auditory attention does not affect the N1 provided that the level of arousal remains the same (Näätänen and Picton, 1987; Picton and Hillyard, 1988). The N1 amplitude is however larger for attended rather than non-attended stimuli when near-threshold intensities are used (Squires et al., 1973) or when other difficult discriminations are required (Picton and Hillyard, 1974). Similarly, selective (sensory channel) attention with supra-threshold stimuli (i.e. attend right-ear stimuli and ignore left-ear stimuli) results in increased N1 amplitude for attended stimuli (Näätänen and Picton, 1987; Picton and Hillyard, 1988).

The average latency of N1 was 137 ms, substantially longer than the usual 100 ms latency. Since the standard stimuli are sufficiently rapid to be perceived as a sustained stimulus, the frequency change is perceived as a brief alteration in the ongoing stimulus and this may evoke a N1 at a longer latency (Linden et al., 1987; Mäkelä et al., 1988). It is also possible that the N1 wave is a mixture of two

different components - the usual N1 response and the mismatch negativity to the frequency change (Näätänen and Picton, 1987).

The P3 amplitude was much larger in the ATTEND than in the IGNORE conditions. This increase in amplitude that occurs when the stimuli are relevant to the subject's task is a characteristic feature of the P3 (Pritchard, 1981; Picton and Hillyard, 1988). The small P3 in the IGNORE condition may have been caused by the the subjects being unable to ignore the targets completely. The P3 latency at Fz was less than at Pz. The shorter latency of the frontal P3 may be ascribed to the presence of P3a, which has a more anterior distribution and a shorter latency than the P3b which predominates posteriorly (Picton and Hillyard, 1988). Other studies however have found the P3 latency at Fz to be later rather than earlier than the latency at Pz (Polich, 1989). The P3 at Fz is small and its latency may vary from one study to another because of overlapping negative waves such as the N2 wave (Fitzgerald and Picton, 1983).

Anesthetized Patients

The N1 and P3 waves (both Fz, Pz) were present for hits during pre-induction, induction and recovery but not during emergence. There were no recognizable waves for misses during induction, surgery and emergence. Our results indicate that auditory endogenous EPs can be recorded in the peri-anesthetic period. The findings are in contrast with the widespread view that the late EPs are too labile to be useful in the presence of anesthetic agents, even in sub-anesthetic concentrations. This view originated from a study which suggested that EPs do not relate to perception because the EPs could not be recorded during low-dose cyclopropane anesthesia even though the stimuli were

above sensory threshold (Clark et al., 1969). Donchin and Sutton (1970) pointed out that the study by Clark et al. (1969) had numerous flaws which could account for the negative results. The major problem was that threshold estimation was carried out at a different time from that of the recording of the EPs. When threshold estimation and recording of the EPs are carried out together there is a good correlation between behavioral performance and the EPs (Hillyard et al., 1971; Squires et al., 1973).

With the exceptions of the hits during emergence and of the misses during recovery the findings are similar to those recorded with near-threshold stimuli during signal detection tasks in awake subjects (Hillyard et al., 1971; Squires et al., 1973): hits produce N1 and P3 waves, whereas misses evoke no recognizable response.

For misses during recovery however there seemed to be a small N1 and possibly a very small P3. The t-tests performed to determine whether the amplitude of these waves were different from zero just fell short of the $P < 0.01$ criterion for significance. Figure 7 shows a reasonably clear N1 for misses during recovery. The discrepancy between the individual measurements and the grand-mean waveforms may in part be due to the use of range measurements. When a wave is present the mean amplitude over a latency range will be less than the peak value. Another possibility is that the analysis of individual measurements included only waveforms based on 6 sweeps or more (to prevent excessive variability) whereas all waveforms were included in the grand-mean waveforms. During recovery misses may therefore have evoked an N1 wave. Squires et al. (1973) postulated that the N1 reflects the amount of signal information that is utilized in the decision process (which is related to the detectability of the stimulus or d' in the language of

signal detection theory (Green and Swets, 1966)) and that the P3 represents the certainty of the decision based on that information. The possible presence of an N1 for misses might mean that the intensity of the stimuli allowed substantial information transfer but that there was some impairment of the decision mechanisms causing failure to detect the targets. Such impairment appears to have been phasic, since periods with high rates for hits alternated with periods where most targets were missed. It is likely that, despite our repeated instuctions, the patients simply forgot the task and ignored the target stimuli. This situation is similar to when the control subjects were asked to read and ignore the stimuli.

Differences between the amplitude of the responses for hits and misses could be evaluated only during induction and recovery. In the other conditions, the number of trials for either hits or misses was too small for analysis. The amplitude of N1 and P3 was larger for hits than for misses but the difference was significant only for the P3 during recovery at both Fz and Pz. The absence of similar significant differences during induction may have resulted from the increased amplitude of the EEG due to thiopental (Clark and Rosner, 1973; Stockard and Bickford, 1981). This causes more variability and reduces statistical power.

Contrary to our expectations, hits during emergence were not associated with identifiable N1 or P3. Only four patients scored hits during emergence and the total number of hits was only 56 resulting in a low signal-to-noise ratio. Furthermore, the signal acquisition was complicated by numerous artifacts due to movements and shivering. Accordingly, the level of residual noise (Fig. 7) for hits during emergence is high. Another possible factor hindering recognition of the

EPs is trial-to-trial latency variability. When the latency and/or shape of a wave varies from trial to trial, the amplitude is artifactually reduced by conventional averaging techniques (Ruchkin, 1988). Single trial analysis (Ruchkin, 1988) could conceivably circumvent the effects of latency variability but might not be applicable in the presence of high amplitude background EEG. In summary, although it is not possible to rule out the presence of small N1 and P3 for hits during emergence the evidence suggests that these components are absent.

This finding is not surprising since the patients may have been responsive but not fully conscious during emergence. It may be possible for a subject to respond to the target stimuli automatically with little if any awareness. Simple auditory detection tasks do not always require full consciousness since they can be performed by subjects who remain in normal stage II sleep (Bonnet, 1982). The isolated forearm test (Tunstall, 1977; Thornton et al., 1989) is probably even less satisfactory than signal detection for assessing awareness. With this test, a tourniquet blocks the arterial flow to the forearm, which is thus not affected by the muscle relaxant. The patient can therefore move the hand to signal "awareness". How to interpret the movements of the hand is a major problem. Patients in neuro-vegetative state may open their eyes and move following auditory stimuli. Such automatic behavior must be ruled out before concluding that a simple hand movement by an anesthetized patient is in response to command and reflects awareness. Indeed it appears very difficult to design a task which would lead to overt actions that would necessarily imply "conscious awareness" (Allport, 1988).

How does the present study relate to published work on the P3 and anesthesia? The available studies are limited to subanesthetic concentrations. Fowler et al. (1988) using a visual linguistic categorization task and single trial analysis (which circumvents the effect of a trial-to-trial latency variability) showed that N_2O 15-35% decreased the amplitude of the P3 by approximately 60% and increased the latency by about 60 ms. These effects were dose-related but there was a ceiling effect for amplitude reduction with N_2O 25%. Estrin et al. (1988) using a pitch discrimination task also found that N_2O (10% to 40%) reduced the amplitude and increased of the latency of the P3. Samra et al. (1988), also using a pitch discrimination task found a 15% increase in latency and 60% decrease in amplitude for the P3 during lorazepam sedation (0.05 mg/kg). The interpretation of the Estrin et al. and Samra et al. findings is difficult because results for hits and misses were pooled. The effect of N_2O and lorazepam may have been less pronounced if based on the P3 for hits only. Earlier work (Lader, 1974; Fenwick, 1979) showed pronounced attenuation of the P3 amplitude with N_2O. The response was virtually abolished with 40% N_2O despite good behavioral performance. These early experiments mainly studied the contingent negative variation and were not well suited for P3 recording (Pritchard, 1981). Adam and Collins (1979) using a complex visual task recorded the P3 during enflurane administration (end-tidal concentrations from 0.12-0.25%). Amplitude of the P3 was markedly attenuated despite adequate task performance. These findings were attributed to trial-to-trial variability rather than to true absence of the P3. Trial-to-trial variability might be greater during complex tasks. Fentanyl (5 μg/kg) significantly reduced the amplitude of the P3

during an auditory oddball task without changing the latency (Velasco, 1984) although the number of missed targets increased. If we exclude studies with protocols not well suited for recording the P3, the evidence from the literature is that the relation between the P3 and target detection remains valid in the presence of low doses of anesthetic agents despite attenuation of the P3 amplitude.

The functional significance of the P3 wave remains uncertain. The P3 may represent access of stimulus information to consciousness or to controlled processing (Hillyard and Picton, 1987). This idea is supported by the observation that the P3 is attenuated during tasks that require rote processing or when the stimuli do not reach consciousness. Even though the elicitation of a P3 depends on the subject's conscious awareness of a stimulus, one however cannot conclude that the cerebral processes manifested by the P3 are necessarily those mediating conscious awareness (Donchin et al., 1983). Other proposals suggest that the P3 reflects revision or updating of memory brought about by unexpected events (Donchin, 1981). Findings that P3 amplitude is larger for stimuli that are better remembered in the future support the memory proposal (Sanquist et al., 1980; Chapman et al., 1981; Karis et al., 1984; Fabiani et al., 1986; Neville et al., 1986). The amplitude of the P3 is largest when the subjects are paying close attention to task-relevant stimuli and when they have high confidence in their decisions (Pritchard, 1981; Hillyard and Picton, 1987; Picton and Hillyard, 1988). The amplitude may, therefore, under certain circumstances at least, reflect the degree of personal involvement with the task.

The P3 wave is emitted when a subject attends to an unpredictable stimulus. Although the presence of a P3 may indicate that the subject is aware of the stimulus, the absence of the P3 does not indicate an

absence of awareness. The stimulus may be predictable or the subject may be attending to something else.

GENERAL DISCUSSION

Before presenting some ideas about how consciousness might be monitored during anesthesia we must examine what "consciousness" means. It is difficult to define consciousness. Natsoulas (1978) discussed seven different meanings of the word consciousness. Three are relevant to the present issue. One meaning associates consciousness with normal wakefulness. This is the usual meaning in anesthesiology and neurology (Plum and Posner, 1982; Bennett, 1987; White, 1987). A second meaning associates consciousness with awareness. Anything may be the object of awareness (hearing a noise, having a thought, etc.). Awareness can be dissociated from wakefulness in both normal subjects and neurological patients. A normal subject can be awake but unaware of certain aspects of his or her environment. The neuro-vegetative patient can be awake but totally unaware. A third meaning associates consciousness with self-consciousness. Self-consciousness refers to being aware of one's own perceptions and thoughts. This self-reflective aspect was emphasized by Klein (1984) who views consciousness as the capacity for reflection in the sense of being able to think about what one knows or perceives. By contrast simple awareness is less personal and less reflective than this third meaning of consciousness. For the rest of the discussion we shall consider consciousness in this third sense and use the terms wakefulness and awareness for the other two meanings.

We propose to associate each meaning with one type of evoked electrical activity. The ASSR may demonstrate that brainstem-cortical interactions are sufficiently organized to allow consciousness in the sense of wakefulness. The ASSR is attenuated during sleep and markedly

reduced during surgical anesthesia. Its reappearance coincides with the return of responsiveness. The N1 and P3 components of the transient auditory evoked potential may demonstrate that the subject is conscious of the stimuli in the sense of being aware. That would explain why the ASSR reappears before the N1-P3 after an anesthetic. During emergence from anesthesia a subject is often conscious in the sense of being awake but not fully conscious in the sense of being aware. One might also speculate that the N1 wave reflects simple awareness whereas the P3 wave reflects full consciousness in the sense of being personally involved in perceiving and remembering the stimulus. These possibilities, however, remain speculative.

What are the similarities between our findings and evoked potentials recorded during sleep? This issue has already been addressed for the ASSR, but not for N1 and P3 waves. The N1 is reduced during non-REM and REM sleep (Williams et al., 1962). Maximal attenuation occurred during sleep stages with higher threshold for awakening by sensory stimuli. This suggests that the reduced N1 amplitude may reflect diminished awareness of external stimuli, a situation similar to what we observed during emergence and recovery. The P3 has, to our knowledge, not been reliably recorded during sleep. Very late (800 ms) positive deflections have been reported (Weitzman and Kremen, 1965) but they do not meet the criteria for P3. The most prominent evoked potential change during sleep is a large negative wave with a peak latency of 300-500 ms (Weitzman and Kremen, 1965; Ujszaszi and Halasz, 1988). This wave, labelled N2, was not observed during our study. There are fundamental differences between sleep and general anesthesia. The two most important are that subjects can be aroused from sleep to

full consciousness by a wide variety of stimuli, and that complex cognitive activity can occur during sleep (Bonnet, 1982).

The distinctions between consciousness, awareness and wakefulness have important implications for the problem of unintentional "awareness" during anesthesia (Bitner, 1983). There are no specific contemporaneous methods for detecting intra-operative wakefulness, awareness or consciousness. Verbal reporting from the patient is currently the only method of establishing that "awareness" has occurred. For the patient to remember some parts of the surgical procedure probably requires the subject to have been conscious at those times since events that are denied conscious attention are probably not available to intentional forms of remembering (Eich, 1984). In all likelihood, there are therefore many instances of wakefulness and awareness during surgery that are not remembered.

Tulving (1985; 1989) has discussed the relationships between memory and consciousness. He proposes three different memory systems: procedural, semantic and episodic. Procedural memory involves simple associations and habits that are learned by repetition. Semantic memory is involved with knowledge about the world; it deals with the recall of facts without any personal involvement. Episodic memory involves the remembering of personally experienced events. Procedural memory does not require consciousness whereas both semantic and episodic memory require consciousness in the laying down of the memory and in the remembering. However, episodic memory requires full consciousness ("personal involvement"). Endogenous EP constitute, in theory, an excellent tool for the detection of unintentional intra-operative awareness or consciousness. Studies in awake controls have repeatedly shown that conscious awareness of a task-relevant stimulus is almost

always associated with P3 provided that the task and recording protocol are adequate (Pritchard, 1981). The main question was therefore whether or not the link between conscious awareness of a target stimulus and the P3 persisted during the peri-anesthetic period. We found that the link was preserved before anesthesia despite the premedication, during induction and in the recovery room. The link is apparently not valid immediately upon emergence from anesthesia although we do not have sufficient data for definite conclusions. The absence of P3 may indicate that the detected change did not reach consciousness despite the motor response. Patients do not usually remember much about what happens during emergence. This may therefore be a period where there is responsiveness but neither clear consciousness nor access to memory.

An interesting question is whether the ASSR during anesthesia is abolished, or only too small for detection. There is evidence that it may persist (Hogan, 1987). Since the transient auditory middle latency response attenuated but not necessarily abolished during anesthesia (particularly below 1.5 MAC), the generation of a steady-state response could be achieved by a slower rate of stimulus delivery (e.g., 20 or 30 sec^{-1} instead of 40 sec^{-1}). The rate of stimulus delivery producing the largest steady-state response could therefore provide information on the level of anesthesia (Brown and Shallop, 1982). For awake subjects, the optimal rate is about 40 sec^{-1} (Galambos et al., 1981; Stapells et al., 1984).

Much research needs to be done before the evoked potentials can be used to monitor consciousness. The practical aspects of recording the evoked potentials pose no major difficulty and automated methods of waveform analysis might render the technique even more practical. Some difficulties will remain, however. Recordings obtained from surgical

patients will tend to be noisier than those obtained in volunteers under ideal laboratory conditions. The interpretation of those recordings will be further complicated by many factors that cannot be completely controlled (pain level, temperature changes, ...). Different anesthetic agents must be evaluated and the time course of recovery of the evoked potentials with each agent must be examined. Much information should come from studying the period of emergence where there are dissociations between different aspects of consciousness.

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