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## Effect of Halothane Anesthesia on the Human Cortical Visual Evoked Response

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The visual evoked response (VER) was monitored in eight women intraoperatively during anesthesia with halothane in oxygen administered via endotracheal tube. Control measurements were made prior to anesthetic induction in these unpremedicated patients. The latency of the positive peak designated P1 increased progressively from a mean of  $113 \pm 10$  (SD) msec in the awake state to the following values at indicated end-tidal halothane concentrations:  $123 \pm 10$  msec at 0.75 per cent;  $130 \pm 9$  msec at 0.90 per cent;  $134 \pm 9$  msec at 1.13 per cent. The differences among mean latency values at these anesthetic concentrations were insufficient to conclude that VER latency would be a useful monitor of anesthetic depth. However, significant effects were seen at clinical levels of halothane anesthesia, and the prolongation caused by anesthesia must be considered when using VERs to monitor central nervous system function during neurosurgery. (Key words: Anesthesia: depth. Anesthetics, volatile: halothane. Brain: electroencephalography; visual evoked response.)

MOST EFFORTS to monitor the brain have employed the electroencephalogram (EEG). The EEG, a complex representation of the overall electrical activity of the brain, lacks specificity. Sensory evoked responses are averaged electrical responses of specific brain areas to repetitive sensory stimuli, and might be a better index of anesthetic effect than the EEG.

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Sensory evoked responses are derived by computer averaging the EEG responses to repeated presentations of a sensory stimulus and statistically removing the random, non-stimulus-related, portion of the EEG.<sup>1</sup> The resultant waveform represents the specific response evoked in the brain by the stimulus. Responses to visual, auditory, and somatosensory stimuli have been studied in this manner. The visual evoked response (VER) was used in the present study. Characteristically, the VER recorded over the occipital lobes following flashes of light contains a prominent positive peak (relative to an "indifferent" electrode positioned over the frontal cortex) with a latency of approximately 100 msec following stimulus onset. This "P100" or "P1" component is presumed to have a neural source within the primary visual cortex (area 17),<sup>2</sup> and has been shown to be a sensitive indicator of visual function.<sup>3</sup> We have been using VERs to monitor the function of the visual system during anesthesia for neurosurgical procedures involving structures in or around the visual pathways. During such procedures, there were qualitative changes in the VERs that had no specific relation to the surgical manipulations, but seemed to be correlated with anesthetic depth.

Domino and coworkers have reported qualitative changes in the VER with premedicants and with variations in depth of halothane anesthesia in man.<sup>4</sup> Burchiel and colleagues described VER amplitude changes during enflurane anesthesia.<sup>5</sup> No systematic work has been done, however, on the relationship between VER characteristics and alveolar halothane concentration. In fact, the review by Clark and Rosner stated that the effects of halothane on sensory evoked responses have received "little attention."<sup>6</sup>

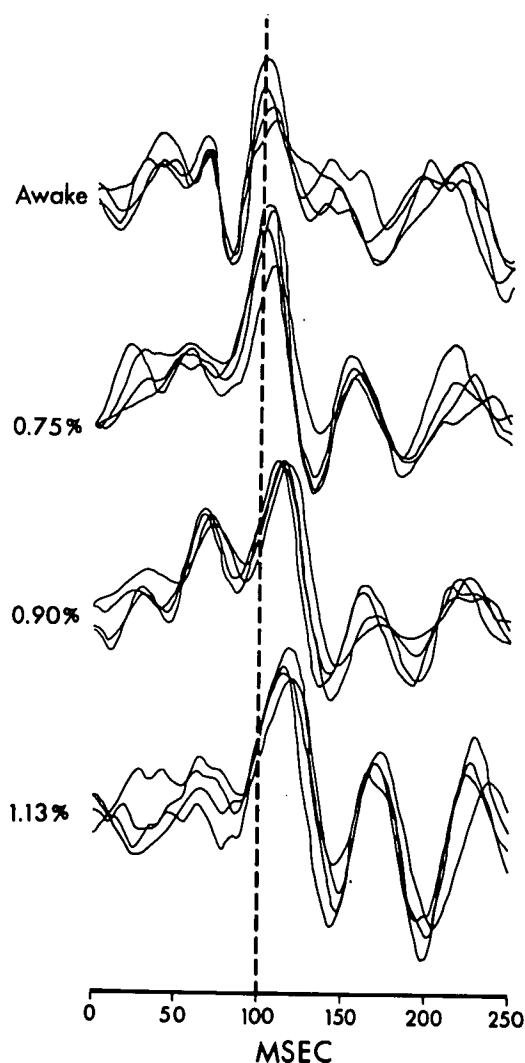


FIG. 1. Waveforms of visual evoked responses from one patient, elicited when awake and anesthetized at three end-expired levels of halothane. Four separate tracings obtained during each condition have been superimposed.

The purposes of our investigation were to answer the following questions: 1) What is the relationship of VER changes to halothane anesthetic depth? 2) When monitoring VER during surgery, what part of a change in VER can be attributed to anesthesia, as opposed to a change resulting from surgical manipulation?

### Materials and Methods

Institutional approval for these experiments was granted by the Human Subjects Review Committee, University of California, Irvine, Medical Center. Eight female patients, aged 23–57 years, gave informed consent to be studied. Their operations were: vaginal hysterectomy (6), abdominal hysterectomy (1), and release of trigger finger (1). They were not premedicated and were brought to the surgical suite early for control studies.

Silver disc electrodes were affixed to the scalp of the vertex, occiput (2.5 cm above theinion), and one mastoid. The EEG recorded between the occiput and vertex (the mastoid electrode serving as ground) was amplified 10,000 times with a bandpass of 1 to 100 Hz by battery-powered amplifiers (Grass Model P-15). Averaged VERs were obtained following 128 monoptic presentations of a visual stimulus using a special-purpose computer (Nicolet Model 1070).

An array of ten light-emitting diodes positioned in two rows on the inside of an opaque eyepatch was illuminated for 30 msec every 500 msec to serve as visual stimulus. The eyepatch was placed over the taped closed eyelid, thus producing a diffuse red flash to the retina. The averaging computer was synchronized to begin sampling at the flash onset and the averaging epoch had a duration of 256 msec following the flash onset.

The VERs were first acquired in the control condition, then at various levels of anesthesia maintained during the operation. Anesthesia was maintained with halothane in oxygen, after paralysis and endotracheal intubation. Early in the study, we found that identical results were obtained when anesthesia had been induced with halothane and oxygen inhalation and after induction with 5–6 mg/kg thiopental. End-tidal halothane concentrations were measured with a calibrated Beckman® LB-2 gas analyzer. Intraoperatively, with controlled ventilation held constant at a tidal volume of 10 ml/kg body weight and a rate of 8 breaths/min, studies were performed at 0.75, 0.90, and 1.13 per cent end-tidal halothane concentrations. The  $P_{aCO_2}$  was not measured. Esophageal temperature was recorded after anesthesia was induced and was maintained between 35 and 36 C by use of a warming blanket. The maximum temperature variation for any patient during VER measurements while anesthetized was 0.4 C.

The VER recordings were initiated at least 30 minutes after induction of anesthesia and, thereafter, when halothane had been maintained at a given concentration for at least 10 minutes. At least four individual VER waveforms were recorded at each concentration. The orders of presentation of the three anesthetic levels differed from patient to patient. When operative time was sufficient to permit it, repeat sets of VERs were obtained at each halothane concentration. The data were averaged for each concentration for each subject and analyzed statistically by a one-way repeated measure analysis of variance. Significance of differences between P1 latency during awake and anesthetized conditions, and among anesthetized levels, was assessed.

To verify that the evoked response was truly stimulus-related, and not systematic artifact, possibly due to sampling rate relative to the EEG slowing caused by

halothane, the eyepatch was removed from the subject, while computer sampling, still synchronized with the flash, continued. The P1 component immediately disappeared.

**Results**

For every patient, VERs were easily obtained. The VER waveforms from one patient are shown in Figure 1. Four replications in the awake condition and at each halothane level have been superimposed to illustrate the reproducibility of the waveform. The primary result of the study is also illustrated in the figure; with increasing alveolar halothane concentration, there was a progressive increase in the latency of the VER components. This is clearly visible in the increasing deviation of the large positive P1 peak to the right of the dashed line at 100 msec as halothane concentration is increased.

The average latencies of the P1 component over at least four replicate VERs for the eight subjects in the awake condition and at three halothane concentrations are presented in table 1. In the awake condition, the mean latency of P1 was 113.2 msec. With increasing end-tidal halothane concentration, the P1 mean latency progressively increased to 133.9 msec at 1.13 per cent halothane. Both 0.90 and 1.13 per cent halothane significantly prolonged P1 latency, compared with awake measurements. The analysis of variance among anesthesia concentrations, excluding awake measurements and thus minimizing any effect of body temperature changes, showed that the influence of anesthetic depth on P1 latency was significant at the  $P < .001$  level. Repeated exposures to given halothane concentrations at various times did not affect P1 latency in any systematic or significant manner.

For some subjects, similar effects were evident in the waveforms for peaks other than P1. This can be seen in the negative and positive peaks following P1 in figure 1. However, those peaks could not be reliably identified in the VER waveforms of all subjects. It should be noted that the later peaks probably are the result of temporally overlapping activity in several cortical areas (including the primary cortex and association cortex), and thus present a more variable picture of the effects of halothane. No systematic change in the amplitude of the VER components as a function of halothane concentration was found.

**Discussion**

There has been interest in using the EEG to determine anesthetic depth since 1950, when Courtin, Bickford, and Faulconer described seven anesthetic depths identifiable by use of the EEG.<sup>7</sup> More recently, power-spectrum analysis of the EEG has facilitated accurate quantification of the EEG, and Bart and coworkers

TABLE 1. Latencies of P1 Component of VERs Obtained at Increasing Depths of Anesthesia

	Latency (msec) Awake	Latency (msec) at Alveolar Halothane (v/v)		
		0.75 Per Cent	0.90 Per Cent	1.13 Per Cent
Subject 1	108	118	135	143
Subject 2	118	124	132	131
Subject 3	107	135	143	139
Subject 4	115	118	126	129
Subject 5	125	133	128	143
Subject 6	100	133	133	137
Subject 7	104	104	111	115
Subject 8	128	121	134	135
Mean	113	123	130	134
SD	±10	±10	±9	±9
P*	—	0.10	0.01	0.01

\* Awake vs. anesthetized.

illustrated variations in power spectra at different inspired concentrations of fluoroene, methoxyflurane and enflurane.<sup>8</sup> The compressed spectral array, a "pictorial" EEG popularized by Bickford,<sup>9</sup> has also been used to demonstrate the EEG frequency changes in response to surgical and anesthetic stimulation, and with changes of anesthetic concentration.<sup>10</sup> Still, the nonspecificity of these methods is troublesome.

Our data indicate that while VERs recorded during surgical anesthesia with halothane are qualitatively very similar to those recorded in the awake condition, the latency of the P1 component is progressively prolonged by increasing alveolar anesthetic concentrations. A means of monitoring anesthetic depth is thereby suggested. Further studies will be necessary to optimize the procedures for such monitoring.

Except for one patient (Subject 8), the latency difference of P1s between awake and anesthetized with 1.13 per cent halothane was greater than 10 msec, which is easily discriminated by this technique, and the maximum shift found in this study was 37 msec. It is common practice in many clinical electrodiagnostic laboratories, including our own, to measure VER latencies to within 2 or 3 msec when evaluating awake patients for optic neuritis. Thus, even with the technique and stimuli used here, it is reasonable that a more thorough and sophisticated procedure for measuring the overall VER latency would considerably increase the sensitivity of the procedure.

In studies of sensory evoked potentials, artifactual results may be obtained due to changes in the sensitivity of the peripheral receptor, in this case, the eye. Possible sources of such errors are changes in pupil size, the direction the eyes are pointed, and the extent of dark adaptation of the retina. The pupil size is of little concern when the stimulus is presented through the closed eyelid. Control studies were also conducted on an awake subject who varied the direction of gaze, behind closed eyelids, and no effect on the P1 latency

was found. The use of a red flash minimized the effect of dark adaptation, which is essentially complete within 10 minutes for such wavelengths. Most importantly, repeated measurements at a given anesthetic level, sometimes separated by 30 minutes or more, showed reproducible results, precluding any effect of dark adaptation or of downward temperature drift.

Our data confirm the observations of Domino and coworkers,<sup>4</sup> who found a qualitative change in the VER waveform with halothane anesthesia. The difference between their experiments and ours is that they used a flash stimulus, whereas we used a diffuse checkerboard pattern. Burchiel and colleagues studied the effects of 2.5–3.7 per cent inspired enflurane on the VER in man and observed a three- to fivefold amplitude increase at normocarbida and a 30–50-fold change with hyperventilation.<sup>5</sup> They concluded that the VER might be useful in studying the epileptogenicity of enflurane. They did not report any latency changes. In contrast to their study, we varied neither body temperature nor ventilation in order to stabilize production and elimination, respectively, of CO<sub>2</sub>.

Adam and Collins,<sup>11</sup> believing that certain late components of the VER measure short-term memory, studied the effects of subanesthetic doses of enflurane on these. At end-tidal enflurane concentration ranges of 0.1 to 0.3 per cent and 0.4 to 0.7 per cent they observed increased latencies in P170 and P250 components of 33 to 36 msec. Their experiment differed significantly from most studies in that the stimulus was a digit flashed before the subject, rather than the conventional flash or checkerboard.

Another variety of evoked response, the auditory brainstem response (ABR), has been recorded during anesthesia. Unlike the VER, which presumably has a cortical origin, it appears that the brainstem response is essentially unchanged during clinical anesthesia.<sup>12</sup> Our unpublished observations confirm these findings.

Siu and associates studied ABRs during open-heart surgery with general anesthesia with diazepam and morphine and found that while ABRs were not affected by anesthesia, decreased body temperature caused significant increases in peak latencies.<sup>13</sup> This was confirmed by Stockard and colleagues, who studied patients anesthetized with nitrous oxide, diazepam, and meperidine for open-heart surgery and also showed that spontaneous hypothermia in the absence of any anesthetic or adjuvant drug produced latency shifts of the evoked potentials.<sup>14</sup> Thus, studies of ABRs should be temperature-controlled. Although qualitative changes in VERs in infants during profound hyperthermia and circulatory arrest have been described,<sup>15</sup> the effects of temperature on normal

adult VERs are unknown. During our study esophageal temperature was carefully maintained between 35 and 36 C.

In summary, these results indicate that halothane anesthesia prolongs the latency of the human VER, an effect that must be considered if the VER is used to monitor the function of the central nervous system during neurosurgical procedures. Also, the data demonstrate a possible use of a direct neurophysiologic response for monitoring anesthetic potency of halothane or other anesthetics. The study also suggests a method for comparative studies of anesthetic agents.

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