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Abstract

To investigate the incidence and manner of auditory information processing during a state of presumed unconsciousness event-related brain potentials (ERPs) were studied in 41 patients undergoing cardiac surgery with propofol/alfentanil anesthesia. The ERPs were recorded during auditory oddball tasks administered before and within several periods of the operation. Mean nasopharyngeal temperature and anesthetic concentrations were determined for each intraoperative ERP recording epoch. During anesthesia ERP waves could still be observed up to 500 ms after stimulus onset indicating that auditory information processing was not suppressed completely by the administered anesthetic agents. Relative to the preoperative recordings, the P1-N1-P2 complex was delayed and more positive going during anesthesia. Comparable changes in ERP morphology have been observed during Stage II–IV sleep, suggesting parallels in the mechanisms underlying early auditory processing in both states of reduced arousal level, possibly related to a selective reduction of a non-specific activity. N1 and P2 peak amplitudes were found to be larger for the deviant tones compared to the standard tones. These amplitude differences most likely reflect automatic detection of stimulus deviance, although it cannot be excluded entirely that they were due to differences in refractoriness. Anesthetic concentrations and nasopharyngeal temperature were found to be of minor significance for ERP control. It is suggested that ERPs could serve as intraoperative reference measures, providing the earliest evidence for auditory processing. This characteristic is important for validation of signals and techniques that are proposed to improve conventional monitoring of anesthesia with respect to detecting unintended awareness. © 1997 Elsevier Science Ireland Ltd.

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1. Introduction

Most studies on changes in event-related potentials (ERPs) during reduced levels of arousal have been focused on natural sleep or sleep-onset (Ogilvie et al., 1991; Campbell et al., 1992; Nielsen-Bohlman et al., 1991; Harsh et al., 1994; Winter et al., 1995). Drug-induced states of diminished arousal levels have received less attention in ERP research. However, they may provide valuable information

about physiological and biochemical mechanisms underlying these diminished arousal levels. In the current study, ERPs were recorded during cardiac surgery with propofol/alfentanil anesthesia to obtain evidence for intraoperative information processing. Earlier indications for preserved perceptual and memory functioning during general anesthesia came from studies using hypnotic regression, intraoperatively presented behavioral suggestions and implicit memory tests (for an overview, see Andrade (1995) and Ghoneim and Block (1992)). These retrospective studies, however, have produced inconsistent results, presumably due to differences in the state of anesthesia at the moment of information presentation. Therefore, it would be useful to examine more directly the processes involved with auditory perception, that is, at the moment that it might actually

occur. In addition, the true incidence of auditory processing during general anesthesia might be evaluated more accurately with an intraoperative instead of postoperative assessment procedure considering the amnesic effects of many anesthetics (Thornton and Newton, 1989).

The recording of cortical auditory evoked potentials (AEPs) has been frequently suggested as a promising method for monitoring intraoperative awareness (Thornton and Newton, 1989; Cluitmans, 1990; Thornton, 1991; Jones, 1994). AEP brainstem components (Wave I–VI) occur within 8 ms following sound onset and reflect activation of the acoustic nerve and different brainstem auditory structures. The midlatency components (No, Po, Na, Pa, Nb) occur between 8 and 40 ms after sound onset and are probably generated in thalamic and cortical auditory structures (Picton et al., 1974). Thornton (1991) and Jones (1994) have demonstrated that AEP brainstem components increase in latency with increased levels of volatile agents whereas they remain unchanged with other anesthetics. In contrast, AEP midlatency components, Pa and Nb in particular, were found to increase in latency and to reduce in amplitude with all examined anesthetics in a dose-related manner (Thornton et al., 1984; Thornton, 1991; Jones, 1994). Furthermore, it has been shown that the Nb component is sensitive to surgical stimulation, showing larger amplitudes during surgery than prior to surgery (Thornton et al., 1988). These results imply that the AEP midlatency components provide significant information about the responsiveness of the auditory neural pathways, making them valuable for monitoring purposes. However, the exact relationship between these AEP parameters and the concrete perception of a stimulus has not yet been established.

AEP midlatency components mark the arrival of sensory information at the primary auditory cortex. Although the occurrence of these components may be a necessary condition for perception it is no guarantee that the presented stimulus will be actually perceived (Jessop and Jones, 1992). There is some evidence that Nb latency may be related to behavioral responsiveness as measured with the isolated forearm technique (IFT), protecting one arm from neuromuscular block (Thornton et al., 1989). In agreement, Schwender et al. (1994) have demonstrated a relationship between Na and Pa latencies and outcomes of an implicit memory task performed after surgery. Additional and more direct evidence for auditory processing, i.e. without confounding influences of motor or memory systems, could be obtained by recording AEP deflections following the midlatency components. These long-latency AEP components, frequently referred to as ERPs, are associated with the cognitive aspects of information processing and are known to be affected by, among others, the subjects' psychological state (Donchin et al., 1978). Such state-related changes in long-latency AEP or ERP components have been described frequently in sleep research. ERP changes due to general anesthesia have been reported only in a small number of recent studies.

In the awake state, early aspects of auditory processing are reflected in the centro-frontal N1 and P2 components, occurring around 100–200 ms post-stimulus (Picton et al., 1974). The amplitudes of these components have been found to vary with the physical and temporal features of the eliciting stimuli as well as by the subjects' attention (Näätänen and Picton, 1987). N1 and P2 are usually studied in conjuction, but by far the most attention is given to the N1 deflection. The multiple processes underlying N1 have been associated with early discrimination processes producing transient detection rather than sheer perception (Parasuraman et al., 1982). Näätänen and Picton (1987) suggested that some of the underlying processes may act as a nonspecific attention trigger, causing the brain to become aware of stimulus information extracted by earlier mechanisms. Other, more specific contributions to N1 may represent the initial readout of information from the sensory analyzers and/or the formation of a neuronal trace in sensory memory (Näätänen and Picton, 1987).

During the process of falling asleep, N1 has been found to decrease in amplitude in parallel with prolonged reaction times (RT) (Ogilvie et al., 1991). With progressing sleep (Stage II–IV) the N1 is usually further attenuated (Nielsen-Bohlman et al., 1991; Campbell et al., 1992) or can even become absent (Paavilainen et al., 1987). In contrast to the N1 response, the following P2 has been found to increase in amplitude at sleep onset (Ogilvie et al., 1991) which proceeded up to Stage II sleep (Nielsen-Bohlman et al., 1991; Winter et al., 1995) and slow-wave sleep (Campbell et al., 1992). Comparable changes in N1 and P2 amplitudes have been observed during general anesthesia. N1 amplitude was found to be reduced during sufentanil anesthesia (Plourde et al., 1993), whereas N1 disappeared entirely during thiopental/isoflurane anesthesia (Plourde and Picton, 1991). In our previous study, reduced N1 amplitudes were found to coincide with enlarged P1 and P2 amplitudes during propofol/alfentanil anesthesia (Van Hooff et al., 1995).

The appearance of a mismatch negativity (MMN) or P3 indicates whether physically deviant stimuli are differently processed. The MMN, reflecting the automatic detection of stimulus deviance, has been occasionally studied during sleep. Paavilainen et al. (1987) and Nielsen-Bohlman et al. (1991) failed to record a MMN during any sleep stage. Campbell et al. (1992) succeeded to do so during REM sleep and Stage II sleep, but the recorded MMN was small and had an atypical early onset. Winter et al. (1995) reported an N1 enlargement for large deviants (1000 Hz difference) during drowsiness, which they explained by an overlap from the MMN. However, a comparable process could not be observed during Stage II sleep (Winter et al., 1995). Nielsen-Bohlman et al. (1991) suggested that the apparent abolition of the MMN during sleep might be caused by an increased noise level, masking the small component. Alternatively, Näätänen and Lyytinen (1995) hypothesized that the attenuation or disappearance of the MMN in sleep might

be caused by a reduced level of cortical activation. The occurrence of a MMN during anesthesia has not been reported in previous literature.

The P3, reflecting controlled stimulus processing and target detection, has been found to gradually disappear during the wake/sleep transition (Harsh et al., 1994; Ogilvie et al., 1991). During sleep positive waves in the 400–800 ms latency range generally appear in response to deviant tones, but it is still uncertain whether or not these positivities correspond with the P3 observed in the awake state (Wesensten and Badia, 1988; Nielsen-Bohlman et al., 1991; Harsh et al., 1994; Winter et al., 1995). Furthermore, the P2 seems to be sensitive for stimulus deviance during Stage II sleep, showing larger amplitudes for the infrequent items (Nielsen-Bohlman et al., 1991; Harsh et al., 1994; Winter et al., 1995). The origin and functional significance of this P2 effect are as yet unknown but its eliciting process may be related to those underlying the awake P3a. Sub-anesthetic concentrations (up to 40% inspired) of nitrous oxide have been found to increase P3 latency (Fowler et al., 1988) and to decrease P3 amplitude (Fenwick et al., 1979) in a dose-dependent manner. With anesthetic concentrations of nitrous oxide, Jessop et al. (1991) did still observe a P300 wave in some of their volunteers in absence of a motor response. Anesthetic concentrations of fentanyl/isoflurane and propofol/alfentanil suppressed the occurrence of a P3 response (Plourde and Picton, 1991; Van Hooff et al., 1995). In contrast, Plourde et al. (1993) claimed to have observed a small P3a wave during some periods of cardiac surgery with sufentanil anesthesia. According to the authors, the occurrence of a P3a may have signaled the regaining of consciousness.

In the present study, ERP changes were investigated during different periods of cardiac surgery with propofol/alfentanil anesthesia. It is an extension of our previous study in which ERPs were recorded from a small group of different patients undergoing the same type of operations (Van Hooff et al., 1995). The main additions with respect to this previous study were:

1. A larger number of patients is examined to improve statistical support, to obtain information about the incidence of auditory processing and to identify intraoperative epochs of particular risk. Note that the 12 patients from our previous study are not included in the current study.
2. Peak instead of mean amplitudes were calculated for the distinguishable peaks to obtain information about changes in latencies and to enable a more precise estimation of the N1 response, which was previously found to be obscured by the preponderant positive ERP waveform (Van Hooff et al., 1995)
3. Nasopharyngeal temperature was recorded in addition to anesthetic concentrations to study possible effects of hypothermia on ERPs.

2. Methods

2.1. Subjects

The study was approved by the local Medical Ethics Committee and informed consent was obtained from 41 patients scheduled for afternoon cardiac surgery (39 coronary-artery bypass graftings and two aortic valve replacements). Only patients who were free from neurological disorders and who had a good left ventricle function were asked to participate. Patients scheduled for emergency or re-operations were not considered. None of the patients reported severe hearing difficulties. Reliable results could be obtained from 40 patients (seven females) with a mean age of 59 years (range: 38–74 years). The mean duration of the operation (from start induction till transport to the Intensive Care Unit) was 3 h 17 min. Pre-operative anxiety scores were obtained the morning of the operation day by means of the Dutch variant of the state-version of the Spielberger State-Trait Anxiety Inventory. One patient was unwilling to fill in this questionnaire.

2.2. Anesthetic technique

Patients were premedicated with subcutaneous morphine 10 mg. Total intravenous anesthesia with propofol and alfentanil was used to induce and maintain general anesthesia. Propofol was administered at an initial rate of 2 mg/kg and alfentanil at 100 μg/kg for the first 12 min. Then the infusion rates were decreased in steps every 10 min to 8 mg/kg/h, 6 mg/kg/h and finally 4 mg/kg/h, for propofol, and to 4 μg/kg/h, 3 μg/kg/h and 2 μg/kg/h, for alfentanil. The last rate for each anesthetic was maintained for the remainder of the operation. Shortly after induction of anesthesia and at the start of cardiopulmonary bypass (CPB), pancuronium 8 mg and cephazolin 1000 mg were given. The lungs of the patients were mechanically ventilated with air and oxygen and ventilation was adjusted to maintain the end-tidal CO_2 at about 4 kPa. Increases in blood pressure were treated with nitroglycerine or ketanserine. Decreases in blood pressure were managed with volume loading, calcium, ephedrine or inotropics as appropriate, together with a reduction in the infusion rates of propofol and alfentanil. Electrocardiogram, arterial blood pressure, ventilation parameters, end-tidal CO_2 tension, O_2 saturation, and temperature were monitored continuously. During CPB slight or moderate hypothermia to 32°C was used.

2.3. Stimuli and apparatus

Tones produced by 100 ms bursts of a digitally stored sine wave (70 dB SPL, rise/fall times 10 ms) were presented binaurally via insert headphones (Nicolet Tip-10) before and during several periods of the operation. The interstimulus interval (ISI) was 1044 ms. Eighty percent of the stimuli were 'standard' 1000 Hz tones, twenty percent were 'devi-

ant' 2000 Hz tones. During two intraoperative oddball tasks five one-syllable words were presented repeatedly intermixed with the two types of tones. In these tasks the words had a probability of 0.15, against 0.70 for the standard tones and 0.15 for the deviant tones. After the operation the presented words were tested for (covert) recognition, which is reported in detail elsewhere (Van Hooff, 1996). In the pre-operative period a total of 200 stimuli were presented. During surgery 400–600 stimuli were presented because of the worse signal-to-noise ratio. An IBM-type 486 Personal Computer provided with a LabMaster AD/DA converter was used for stimulus presentation, experimental control and data acquisition.

2.4. Physiological recording

The electroencephalogram (EEG) was recorded from Ag–AgCl electrodes placed at Fz, Cz, Pz and two lateral positions located midway between T3-C3 (C5) and T4-C4 (C6), approximately over the temporal auditory projection areas. Linked pre-auricular points served as reference. Inter-electrode impedances were less than 3 kΩ. During preoperative measurements the EOG was recorded by three pairs of electrodes, two pairs for vertical movements (supra and infra orbital ridges of each eye) and one pair for horizontal movements (at the outer canthi). During the intraoperative measurements the EOG was not recorded because eye movements were not expected. The patients received muscle relaxants and their eyelids were closed with adhesive tape. EEG and EOG signals were amplified using a 14-channel Nihon Kohden electroencephalograph (time constant 6.6 s, lowpass filter −3 dB cut-off at 35 Hz). The amplified signals were digitized on-line with a sample frequency of 125 Hz (resolution 12 bit). During the entire operation, mean nasopharyngeal temperature was copied every 10.24 s from the anesthesia monitor using a HP 78360 Careplane interface board.

2.5. Procedure

Baseline recordings were obtained the morning of surgery before the patients received their premedication. Patients were seated in a wheelchair in a quiet separate recovery box on the intensive care unit. They were asked to relax as much as possible, to close their eyes and to ignore the presented tones during the oddball task. During anesthesia, oddball tasks were administered during the following periods: (i) before CPB (approximately 30 min after first incision), (ii) at the start of CPB, (iii) at the end of CPB and (iv) about 10 min after CPB. The oddball tasks consisting of tones and words were administered during the first (i) and third (iii) period. During longer lasting operations intermediate recording periods were also obtained. The exact period of recording was dependent on the absence of disturbances due to electro-surgery or the bypass pump. The total duration of one ERP recording period varied from 4 to

15 min. During or close to the ERP recordings bloodsamples were taken for analysis of propofol and alfentanil plasma levels.

2.6. Data analysis

Pre-operatively recorded EEG signals were first corrected for eye-movements using the method of Van de Berg-Lenssen et al. (1989). The EOG-corrected and intraoperative data were digitally filtered using a 33-point finite-impulse response band-pass filter with −3 dB cut-off frequencies of 2.5 and 8 Hz. EEG trials contaminated by artifacts were automatically rejected. Criteria to detect an artifact were the occurrence of spikes greater than 100 μV, drift greater than 80 μV in a single trial, or a difference in mean amplitude of four successive 250 ms epochs with the 200 ms prestimulus baseline greater than 60 μV. The accepted EEG signals were averaged for each channel time-locked to the onset of the stimuli. Each ERP waveform consisted of at least 40 trials and were obtained from a recording period not longer than 15 min in order to keep recording circumstances as stable as possible. ERP waveforms were obtained for standard tones, deviant tones and words separately.

ERP peak amplitudes and latencies were defined for each individual trace as indicated in Table 1. Time-windows were selected such that they enclose the distinguishable peaks in the grand averages. P1 amplitudes were determined relative to the pre-stimulus baseline. N1 and P2 were determined with respect to their preceding peak (P1N1 and N1P2, respectively). The intraoperative waveforms remained practically below baseline level and peaks were not always clearly recognizable. They were nevertheless calculated to obtain information about changes in peak latencies and inter-peak relationships. It was assumed that amplitudes would approach zero when no clear peak could be identified. Latency results, however, have to be interpreted with care for this reason. Using peak measures to quantify ERPs is common practice in both sleep and anesthesia research (Harsh et al., 1994; Nielsen-Bohlman et al., 1991; Plourde et al., 1993). Peak amplitudes are considered more sensitive than mean amplitudes because they are less affected by variance in latency and slope, and because they do not integrate data over a certain fixed

Table 1

Definition of peak and mean amplitudes for the different recording periods.

Component	Preoperative	Intraoperative
P1 peak	Max. 0–75 ms	Max. 0–125 ms
N1 peak	Min. 75–150 ms	Min. 125–275 ms
P2 peak	Max. 150–275 ms	Max. 275–450 ms

Note. Individual peak amplitudes were defined as the maximal (P1,P2) or minimal (N1) values in the indicated intervals. P1 amplitudes were determined in respect to the pre-stimulus baseline. N1 and P2 were determined with respect to their preceding peak (P1N1 and N1P2 respectively). Peak latencies were all measured relative to stimulus-onset.

time interval. In addition, peak measures would allow us to specify criteria to evaluate whether or not a P1-N1-P2 complex could be distinguished in the ERP trace (see next section). The ERP waveforms to words were ambiguous and separate peaks could usually not be identified. Consequently, it was not possible to quantify reliably these waveforms. For this reason, ERPs to words are not discussed in the remainder of this paper[2].

ERP amplitudes and latencies were used as dependent variables in statistical analyses, using the SPSS-PC statistical package. MANOVAs with repeated measures were used to analyze differences between ERPs in response to frequent and infrequent tones in each recording period, ERP differences between the preoperative recording and the first intraoperative recording (before CPB), and ERP changes during the operation. Although in these analyses repeated measures analysis of variance designs were used, the multivariate test of significance was selected to circumvent the problem of violating the sphericity assumption (Jennings, 1987; Vasey and Thayer, 1987). In each case the approximate *F*-value associated with the multivariate test is reported. To specify the influence of the anesthetic agents and temperature, correlations were calculated between ERP measures and propofol and alfentanil plasma concentrations and between ERP measures and mean nasopharyngeal temperature. To obtain information about the incidence of intraoperative ERPs, criteria were specified to judge whether or not a clear ERP waveform could be distinguished in the individual recordings. Because the ERP responses were most clearly visible at Cz and because the recordings in response to frequent stimuli had the best signal-to-noise ratio, the criteria were applied to the Cz recordings in response to frequent tones only. The criteria were based upon the median P1N1 amplitude (larger than 1.46 μV), the median N1P2 amplitude (larger than 1.73 μV) and the correlation with an overall average waveform obtained by averaging the post-stimulus EEG over all intraoperative recording periods (*r* larger than 0.55). When a recording met all these criteria it was considered a credible ERP response, i.e. containing a recognizable P1-N1-P2 complex.

3. Results

Grand average waveforms from the midline electrode positions obtained during the distinct recording periods are shown in Fig. 1. They are composed of different numbers of individual ERPs because reliable data could not always be obtained from all patients. During anesthesia there was a high variability of individual ERPs which has decreased the amplitudes of the different waves in the grand-averages. In several cases ERP traces were practically flat, whereas sometimes peak-to-peak amplitudes

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[2] For illustrations and descriptions of the ERPs the reader is referred to Van Hooff et al. (1996).
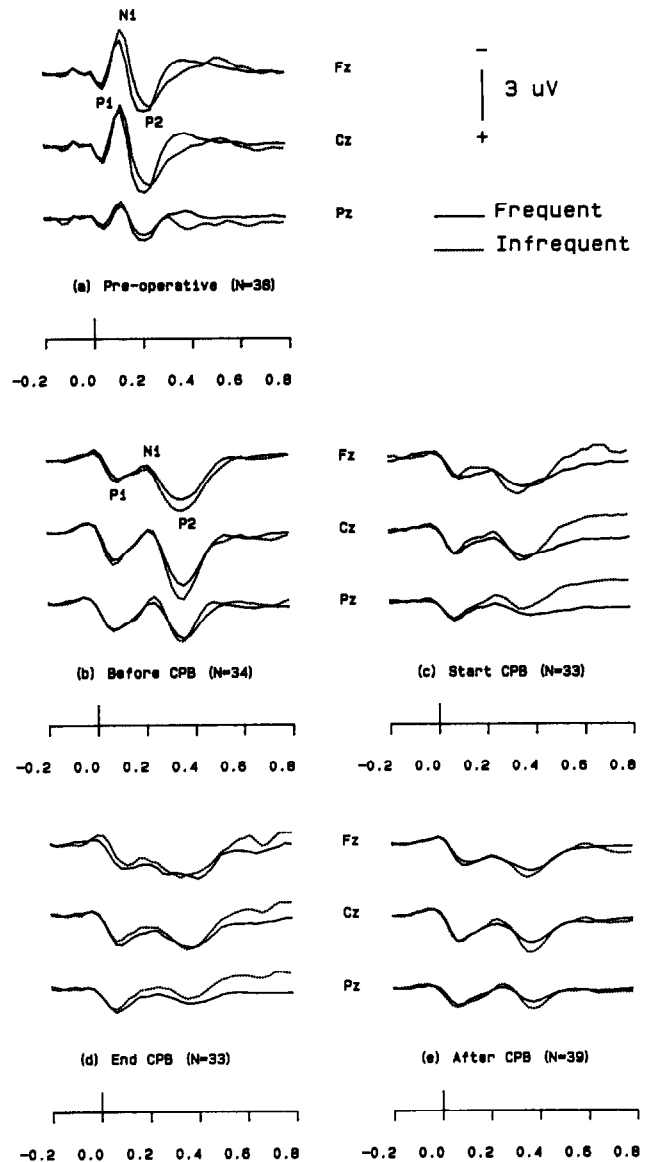
Fig. 1. Grand average ERP waveforms to frequent tones (solid line) and infrequent tones (dotted line) recorded from the three midline electrode positions during oddball tasks administered (a) the morning of the operation day, (b) before CPB, approximately 30 min after first incision, (c) at the start of CPB, (d) at the end of CPB, and (e) approximately 10 min after CPB.

could be observed that were about twice as large as in the awake state. From the intraoperatively recorded ERPs, those recorded before CPB appeared to have the largest amplitudes. Compared to the preoperative ERPs the intraoperative ERPs were delayed and more positive going. The N1 wave, prominently present in the preoperative recordings, dropped below pre-stimulus baseline during anesthesia, but seemed to remain partially sensitive for stimulus deviance, particularly at the start and end of CPB (Fig. 1c,d). The P2

Table 2

Multivariate F-values for the factor stimulus probability (frequent versus infrequent tones) and for the Stimulus probability × Electrode position (Fz, Cz, Pz) and Stimulus probability × Hemisphere (C5, C6) interactions for P1N1 and N1P2 amplitudes

Period	df	P1N1		N1P2	
		Midline	Lateral	Midline	Lateral
Stimulus probability					
Preoperative	1,37	18.97***	28.31***	4.07	4.33*
Before CPB	1,33	12.95**	18.52***	22.18***	18.80***
Start CPB	1,32	65.60***	58.02***	54.73***	31.10***
End CPB	1,32	15.16***	10.94**	26.20***	30.25***
After CPB	1,38	13.61**	25.36***	27.48***	39.20***
Stimulus probability × Electrode position/Hemisphere interaction					
Preoperative	2,36/1,37	9.34**	6.24*	6.48**	<1
Before CPB	2,32/1,33	<1	<1	9.71**	<1
Start CPB	2,31/1,32	4.81*	2.20	23.50***	<1
End CPB	2,31/1,32	8.29**	<1	8.76**	<1
After CPB	2,37/1,38	7.51**	6.33*	4.00*	8.09**

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. For the midline electrode positions (Fz,Cz,Pz) the multivariate F-values for the Stimulus probability × Electrode position interaction are given in the lower part of this table, while for the lateral electrode positions (C5,C6) the multivariate F-values for the Stimulus probability × Hemisphere interaction are given.

wave decreased less in amplitude than N1 and showed slightly larger amplitudes for the infrequent tones than for the frequent tones in all but the third intraoperative recording period (Fig. 1b,c,e).

In total, 176 ERPs could be recorded during the 40 operations. In about half of the patients an extra oddball task could be administered during CPB (in addition to those administered at the start and end of CPB). The mean duration of an intraoperative recording period was 10 min 36 s (SD = 2 min 23 s). The mean number of trials composing ERPs in response to frequent tones and infrequent tones was 364 (SD = 85) and 87 (SD = 23) respectively.

3.1. Scalp distribution and effects of stimulus probability

Separate MANOVAs were carried out for each recording period to examine effects of stimulus probability (frequent versus infrequent) and electrode position (Fz, Cz, Pz). Similar MANOVAs were carried out for the lateral electrode positions with stimulus probability and hemisphere (C5 vs. C6) as within subjects factors. The effects of stimulus probability on P1N1 and N1P2 amplitudes are summarized in Table 2. For the midline electrode positions, the mean values of P1N1 and N1P2 amplitudes are given in Fig. 2 as a function of recording period and stimulus probability. Probably because of individual variance in latency and slope of the different peaks, these mean values showed larger amplitude differences than the grand averages of Fig. 1 (see Fig. 4 for individual examples). Unexpectedly, P1N1 and N1P2 showed relatively large amplitude differences at the Fz electrode position at the start and end of CPB. This might be due

to interference of the bypass pump, introducing peaks in the individual recordings that could not be averaged nor filtered out sufficiently for the infrequent stimuli. Electrode position and hemisphere effects are given in Table 3. Latencies of the different peaks at Cz for frequent and infrequent stimuli are presented in Table 4.

Pre-operatively recorded ERPs of 38 patients were analyzed. For one patient it was not possible to administer the pre-operative oddball task because of limited time and for another patient the results were omitted because of inaccurate stimulus presentation. A clear P1-N1-P2 complex could be observed in the ERPs to both the frequent and infrequent tones. Stimulus probability did affect P1 and P1N1 amplitudes, showing larger amplitudes for the infrequent tones. The latencies of P1, N1 and P2 were significantly longer for the infrequent tones compared to those for the frequent tones (Table 4). A prolonged positivity could be observed exclusively in the ERPs to infrequent tones (Fig. 1). This positivity was most apparent at the Cz electrode position and probably corresponds to a partial P3a. Similarly, the prolonged duration of the N1 for infrequent tones might result from an added negativity, possibly corresponding to the MMN.

During anesthesia P1-N1-P2 waveforms were present for both the frequent and infrequent tones. P1N1 and N1P2 amplitudes were larger for infrequent than frequent tones during all intraoperative recording periods (Fig. 2). These amplitude differences were largest at the Fz and Cz electrode positions, as could be revealed from significant Stimulus probability × Electrode position interactions (Table 2). Significant effects of stimulus probability on peak latencies were found exclusively for P1 at the end of CPB ($F(1,32) = 10.64$, $P < 0.01$), showing shorter P1 latencies for the infrequent stimuli (Table 4).

3.2. Differences between ERPs recorded before the operation and before CPB

For 32 patients differences between ERPs recorded before the operation and before CPB (the first intraoperative recording period) were analyzed. Separate MANOVAs were carried out for midline and lateral electrode positions. Effects of recording period on ERP amplitudes are summarized in Table 5 (left two columns). To test true differences in midline scalp distribution, the analysis was also performed with normalized data, computed by dividing the obtained amplitude measures by the square root of the sum of squared amplitudes over all three midline electrode locations (McCarthy and Wood, 1985). Relative changes in peak amplitudes involved with the transition to anesthesia are visualized in Fig. 3. In this figure the mean amplitudes of the preoperative recordings were taken as the 100% level.

Relative to the preoperative recordings both P1 amplitude and P1 latency (Midline: $F(1,31) = 151.58$, $P < 0.001$; Lateral: $F(1,31) = 157.55$, $P < 0.001$) increased during anesthesia. Concerning the midline electrode positions, the
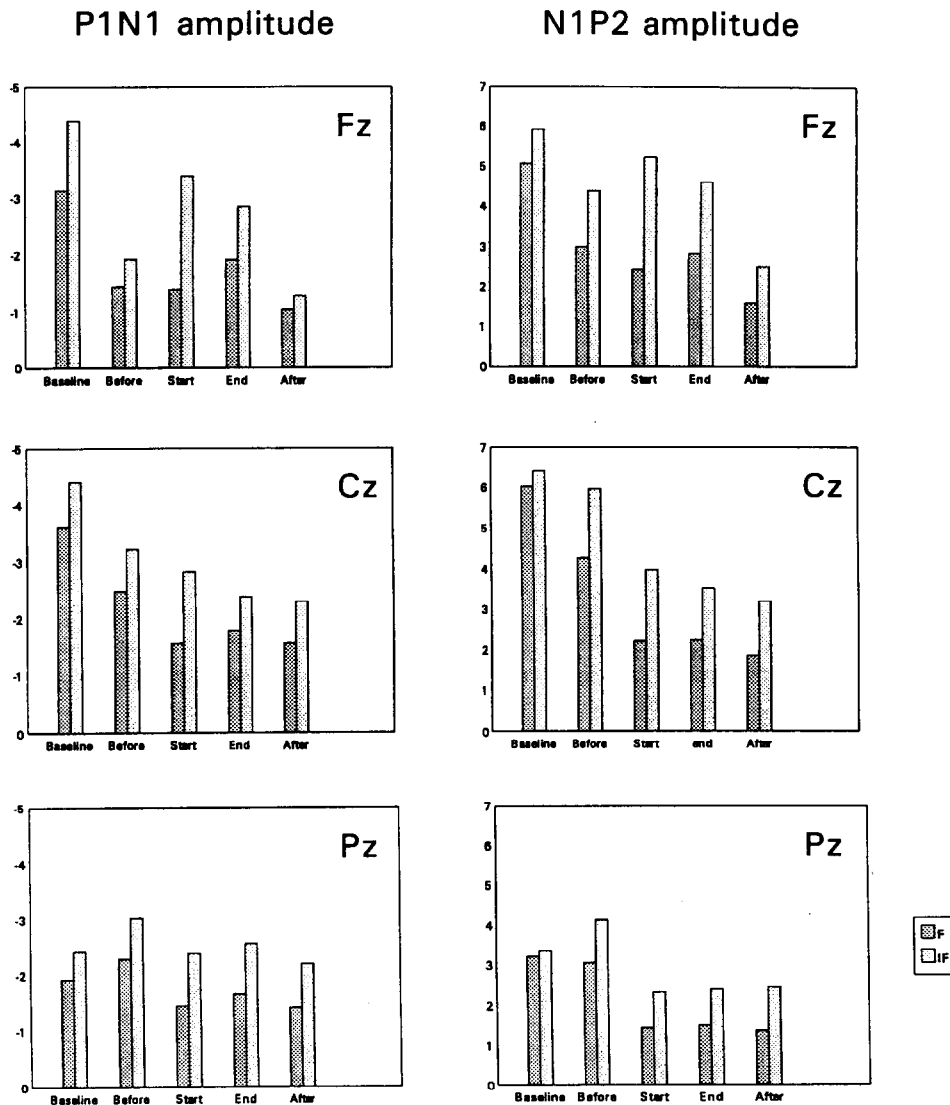
P1N1 amplitude

N1P2 amplitude

Fig. 2. Mean P1N1 and N1P2 amplitudes (in μV) for frequent (dark) and infrequent (light) tones from the midline electrode positions for each recording period. Baseline, preoperative recording period; Before, before CPB; Start, start CPB; End, end CPB; After, after CPB.

P1 amplitude increase was the largest for Pz and the smallest for the Fz electrode position (Fig. 3). For P1 latency the opposite effect was observed: P1 latency increased the most at Fz and the least at Pz (Recording period × Electrode

position: $F(2,30) = 6.52$, $P < 0.01$). The difference in amplitude increase for the distinct electrode positions resulted in a change in P1 scalp distribution. Before the operation P1 had a fronto-central maximum whereas before

Table 3

Electrode-position and hemisphere effects for the peak amplitudes of the different ERP peaks recorded during the distinct recording epochs.

	Preoperative (N = 38)	Before CPB (N = 34)	Start CPB (N = 33)	End CPB (N = 33)	After CPB (N = 39)
P1 peak	Cz > Fz > Pz***	Cz > Pz > Fz***	Fz/Cz > Pz***	Fz/Cz > Pz**	Cz > Fz/Pz***
	ri > le***	ri > le***	ri>le***	ri > le***	NS
P1N1	Cz/Fz > Pz***	Cz/Pz > Fz***	NS	NS	Cz/Pz > Fz***
	ri > le***	ri>le***	ri > le***	ri > le***	ri > le***
N1P2	Cz/Fz > Pz***	Cz > Fz/Pz***	Fz > Cz > Pz***	Fz > Cz > Pz***	Cz > Fz > Pz***
	NS	NS	NS	ri > le***	ri >le***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. NS, not significant; ri, right (C6); le, left (C5). Description of the electrode position effects are derived from inspection of the mean amplitudes. '>' more positive for P1 and N1P2 but more negative for P1N1.

Table 4

Mean P1, N1 and P2 latencies (in ms) from Cz for the frequent and infrequent stimuli

Recording period	ERP peak	Frequent stimuli	Infrequent stimuli
Preoperative	P1	34 (13)	38 (16)*
	N1	107 (11)	117 (14)***
	P2	206 (25)	226 (32)**
Before CPB	P1	85 (27)	76 (26)
	N1	216 (39)	202 (45)
	P2	356 (37)	360 (47)
Start CPB	P1	71 (19)	69 (27)
	N1	201 (49)	213 (45)
	P2	365 (52)	363 (55)
End CPB	P1	88 (23)	71 (36)**
	N1	201 (47)	205 (53)
	P2	353 (57)	365 (49)
After CPB	P1	82 (18)	76 (26)
	N1	216 (54)	213 (51)
	P2	358 (55)	355 (53)

Standard deviations are given in parentheses. Note that the standard deviations were generally larger during surgery than before surgery.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

CPB it had a centro-parietal maximum. The Recording period × Electrode position interaction remained significant after normalization of data ($F(2,30) = 3.37, P < 0.05$), suggesting a true difference in P1 scalp distribution. The right hemisphere dominance of P1 was larger during anesthesia than before anesthesia.

P1N1 was clearly affected by anesthesia, showing smaller amplitudes during the operation. At Fz and Cz electrode positions P1N1 amplitude decreased to approximately 50% and 75% of the preoperative values, respectively. At Pz P1N1 showed a slight increase in amplitude (Fig. 3). As a result P1N1 scalp distribution changed from fronto-central before the operation towards centro-parietal during anesthe-

sia. Because the Recording period × Electrode position interaction remained significant after normalization of data ($F(2,30) = 25.90, P < 0.001$), it reflects a true difference in P1N1 scalp topography. A Recording period × Hemisphere interaction revealed that the right hemisphere dominance of P1N1 was larger during anesthesia than before anesthesia. N1 latency was prolonged during anesthesia (Midline: $F(1,31) = 346.29, P < 0.001$; Lateral: $F(1,31) = 213.11, P < 0.001$), particularly at Cz and Pz electrode positions (Recording period × Electrode position: $F(2,30) = 17.59, P < 0.001$).

N1P2 amplitude decreased during anesthesia at the lateral electrode positions but not at the midline electrode positions. A Recording period × Electrode position interaction revealed a change in N1P2 scalp distribution from the awake to the anesthetic state (normalized data: $F(2,30) = 9.12, P < 0.01$). Before the operation P2 had a fronto-central dominance, whereas before CPB P2 had the largest amplitudes at Cz. P2 latency was prolonged during anesthesia (Midline: $F(1,31) = 506.48, P < 0.001$; Lateral: $F(1,31) = 277.00, P < 0.001$).

3.3. ERP differences between the intraoperative recording periods

Additional analyses were performed to examine ERP differences between the four intraoperative recording periods ($N = 26$). This was done for the midline and lateral electrode positions separately (Table 5, right two columns). P1 amplitude remained approximately the same during the operation. Its midline scalp distribution varied slightly during this period. P1 latency varied during the operation at the midline electrodes, showing shorter latencies during CPB than before and after CPB ($F(3,23) = 3.39, P < 0.05$).

P1N1 amplitude obtained from the midline electrode positions varied during the operation. The amplitude varia-

Table 5

Multivariate F-values for the factor recording period and for the Recording period x Electrode position (Fz, Cz, Pz) and Recording period × Hemisphere (C5,C6) interactions for P1, P1N1 and N1P2 amplitude

	Preop. vs before CPB		Intraop. periods	
	Midline	Lateral	Midline	Lateral
Recording period				
df	1,31	1,31	3,23	3,23
P1	13.95**	9.90**	1.37	<1
P1N1	7.64*	22.90***	5.54**	1.91
N1P2	1.10	14.68**	8.59**	6.64**
Recording period × Electrode position/Hemisphere interaction				
df	2,30	1,31	6,20	3,23
P1	4.26*	8.16**	3.70*	<1
P1N1	27.45***	26.21***	10.84***	<1
N1P2	13.45***	<1	9.68***	1.36

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. The left two columns present MANOVA results for data obtained before the operation and before CPB. The right two columns present MANOVA results for data obtained within the four distinct intraoperative recording epochs. For the midline electrode positions (Fz,Cz,Pz) the multivariate F-values for the Recording period × Electrode position interaction are given in the lower part of this Table, while for the lateral electrode positions (C5,C6) the multivariate F-values for the Recording period × Hemisphere interaction are given.

RELATIVE AMPLITUDES

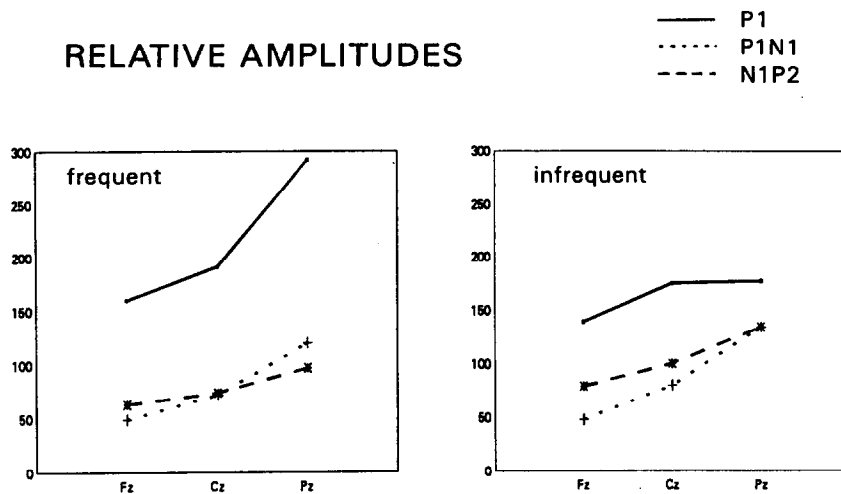———— P1
······ P1N1
- - - - N1P2

Fig. 3. Relative amplitudes and latencies for midline P1 (solid line), P1N1 (dotted line) and N1P2 (dashed line), recorded before cardiopulmonary bypass, displayed in percentages of the preoperative values. Percentages below 100 mean a decrease with respect to the preoperative values and vica versa.

tion was different for the distinct electrode positions ($F(6,20) = 10.84$, $P < 0.001$) and type of stimuli ($F(3,23) = 4.72$, $P < 0.05$). In general, P1N1 had the largest amplitude before CPB. From the start of CPB P1N1 remained approximately the same with a slight decrease in amplitude after CPB. The P1N1 amplitude obtained from the lateral electrode positions did not change during the operation. N1 latency showed no variations during the operation.

N1P2 amplitude also varied during the operation. In correspondence with P1N1, N1P2 had the largest amplitude before CPB and smallest amplitude after CPB. N1P2 had a different midline scalp distribution during CPB than before CPB and after CPB which especially held for the infrequent stimuli (three-way interaction: $F(6,20) = 7.75$,

$P < 0.001$). There were no significant effects on P2 latency during the operation.

3.4. Correlation ERP parameters and propofol-alfentanil plasma levels

Correlations were calculated between ERP amplitudes and latencies obtained from the midline electrode positions and the logarithm of propofol and alfentanil plasma levels. Only those ERP measurements were included when bloodsamples were taken not more than two minutes before the start of a measurement or not more than two minutes after the end of a measurement. Typically, the bloodsamples were taken during the ERP recording. Mean time between sample taking and start or end of recording was 9.4 s

Table 6

Correlation coefficients between propofol and alfentanil plasma levels and ERP peak amplitudes and latencies during the periods before ($N = 31$), during ($N = 60$), and after ($N = 31$) cardio-pulmonary bypass (CPB)

ERP peak	Before CPB			During CPB			After CPB		
	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
Propofol									
P1 latency	0.3286*	−0.0321	0.0404	0.0309	−0.0542	−0.1291	0.2694	−0.0710	−0.1959
P1 peak amplitude	0.1860	0.1426	0.1282	−0.1177	−0.2799*	−0.1940	−0.0005	−0.2035	−0.1957
N1 latency	0.0242	−0.0647	−0.0091	0.0448	−0.1713	−0.0932	−0.0719	−0.1256	−0.1803
P1N1 amplitude	0.0374	0.0952	−0.0198	0.0852	0.2261*	0.1569	0.1183	0.1714	0.1371
P2 latency	−0.1809	−0.0948	0.0736	0.3199**	0.3806**	0.2298*	−0.1926	−0.1667	−0.0422
N1P2 amplitude	−0.1932	−0.1920	−0.1214	0.2015	0.1157	0.0418	−0.1100	−0.0188	0.0826
Alfentanil									
P1 latency	0.0274	−0.3775*	−0.3379*	−0.0480	−0.1050	−0.0692	0.2535	−0.2045	−0.2682
P1 peak amplitude	0.1275	−0.0526	−0.1187	−0.0226	0.0531	0.1392	0.0356	−0.1050	−0.1947
N1 latency	0.1066	0.1141	0.1205	−0.1076	−0.0418	−0.0668	−0.1028	−0.1279	−0.0504
P1N1 amplitude	0.1427	0.1034	0.0842	0.1578	0.0537	−0.0255	0.1243	0.0834	0.1033
P2 latency	−0.0677	0.0256	−0.2205	0.0233	0.0795	0.1066	−0.1773	−0.1386	−0.2884
N1P2 amplitude	−0.2617	−0.2029	−0.2061	0.0733	0.0042	−0.0391	−0.0791	−0.0013	0.0436

*$P < 0.05$, **$P < 0.01$.

Table 7

Mean nasopharyngeal temperature (in °C) during the different recording periods and correlations with ERP amplitudes and latencies

ERP peak	Latency			Amplitude		
	Fz	Cz	Pz	Fz	Cz	Pz
P1	0.2824***	0.1995**	0.1890**	0.1439*	0.1887**	0.2116**
P1N1	0.2406**	0.2266**	0.3481***	−0.1635**	−0.1995**	−0.3066***
N1P2	0.2244**	0.3030***	0.3478***	0.2413**	0.2537**	0.2750***

Mean (SD) for each period: Before CPB, 35.01 (1.05); Start CPB, 33.51 (2.12); End CPB, 34.70 (2.23); After CPB, 35.16 (1.62).
$*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

(SD = 25.2). Because CPB disrupts both pharmacokinetic and pharmacodynamic processes (Russell, 1991), separate correlations were calculated for the period before CPB, the period during CPB and the period after CPB (Table 6).

Overall analysis, incorporating the total number of measurements across all recording epochs, revealed that P2 latency at Cz correlated with propofol blood levels ($r = 0.23$, $P < 0.01$), having somewhat longer latencies with higher propofol concentrations. From the separate analysis it became evident that before CPB P1 latency increased with higher concentrations of propofol at the Fz electrode position. During CPB low but significant correlations with propofol concentration were found for P1 amplitude (Cz), P1N1 amplitude (Cz), and P2 latency (Table 6). Because P1N1 is defined as a negative amplitude, these correlations indicate that both P1 and P1N1 had smaller amplitudes with higher propofol concentrations. Alfentanil was found to correlate slightly with P1 latency (Cz: $r = -0.1592$, $P < 0.05$). From the separate analyses it became evident that this correlation was most manifest before CPB, showing shorter latencies at Cz and Pz with higher concentrations of alfentanil.

3.5. Correlation ERP parameters and nasopharyngeal temperature

Patients were slightly or moderately cooled during CPB, depending mainly on the type of operation and surgeon on duty. For 16 recordings the nasopharyngeal temperature was unreliable due to superficial intrusion and were therefore excluded from further analysis. For the other recordings the mean nasopharyngeal temperatures were calculated by averaging the values obtained every 10.24 s over the entire ERP recording epoch. Correlation analyses revealed low but significant correlations between mean nasopharyngeal temperature and all ERP measures (Table 7). With increased temperatures latencies became longer and amplitudes became larger.

3.6. Incidence of ERPs during anesthesia

By using our previously-formulated criteria 44 from the 176 recordings were judged as containing a recognizable P1-N1-P2 complex (25%). Most of these recognizable ERP waveforms were recorded before CPB. The percen-

tages of reliable ERPs in each recording period were 52% before CPB, 18% at the start of CPB, 33% at the end of CPB, and 21% after CPB. Fig. 4 presents the grand averages for the positively and negatively classified ERPs and some individual examples of each category. Note that there is a large inter-subject variability in latency and slope of the different peaks and in the effect of stimulus deviance. Furthermore, the averaging procedure clearly has had a 'smoothing' effect on the waveforms as well as on the differences due to stimulus deviance.

Concentration of propofol was similar between those periods in which recordings contained a clear ERP (2.29 μg/l,
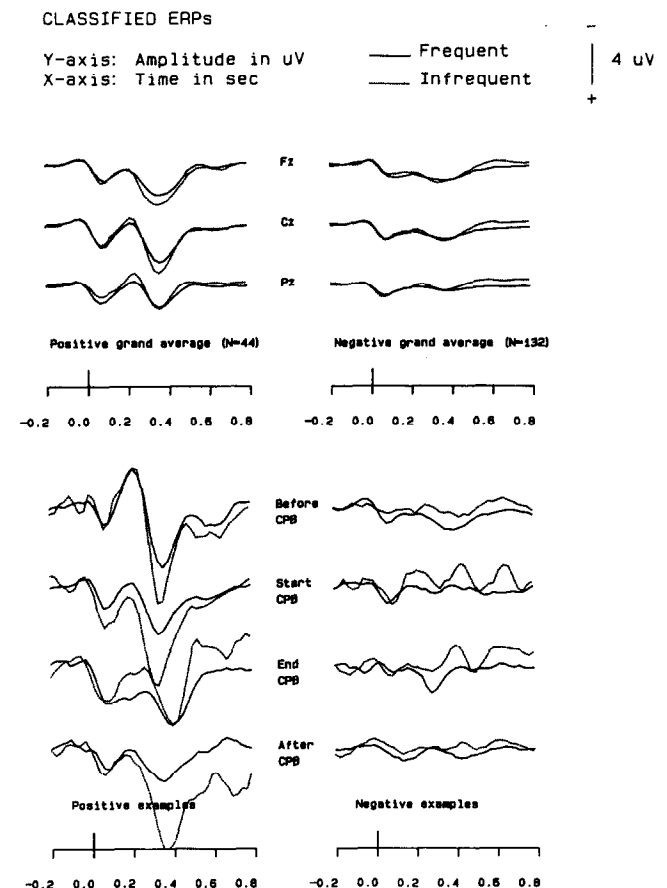

Fig. 4. (Top) Grand average waveforms for positively and negatively classified ERPs according to our criterium (see text). (Bottom) Examples of individual waveforms obtained from eight different patients which were judged as clear ERPs (left) or no clear ERPs (right).

SD = 1.34) and those containing no clear ERP (2.00 μg/l, SD = 0.75) (t = 1.50, df = 41.1, P = 0.247). Alfentanil blood levels were also not significantly different for recordings containing an ERP (459 ng/l, SD = 145) and those containing no ERP (436 ng/l, SD = 124) (t = -0.88, df = 122, P = 0.378). Nasopharyngeal temperature was slightly higher during the recording of credible ERPs (34.8 C°, SD = 2.31) than during the recording of non-recognizable ERPs (33.9 C°, SD = 2.23) (t = 1.94, P = 0.054). In twelve patients no clear ERPs could be recorded during any of the intraoperative recording periods (30%). These patients did not differ from the other patients (N = 28) with respect to age (t = 0.67, df = 38), anxiety score (t = 0.62, df = 37), duration of operation (t = 0.79, df = 38) and duration of CPB (t = 1.28, df = 38). They also did not show any specific impairments the morning after surgery.

4. Discussion

In agreement with our preliminary study (Van Hooff et al., 1995), ERP waves could be observed during anesthesia up to 500 ms after stimulus onset. This suggests that auditory information not only arrived at the cortex but was also processed up to a certain level of cognition, at least in a number of patients. Furthermore, the increased latencies of P1, N1 and P2 indicated a general slowing of auditory processing. The morphology of the intraoperatively recorded ERPs differed from those recorded in the awake state, but comparable changes in these early ERP deflections are reported in sleep research (Campbell et al., 1992; Nielsen-Bohlman et al., 1991; Winter et al., 1995). This suggests possible parallels in the mechanisms underlying primary auditory processing in both states of diminished arousal levels. During anesthesia P1N1 and N1P2 amplitudes were larger for the infrequent tones compared to those for frequent tones, which might reflect a preserved ability to detect stimulus deviance.

During anesthesia N1 amplitudes were found to be attenuated to near baseline levels. This was only partly due to the simultaneous increment of the P1, because N1 was measured with respect to this preceding peak instead of to the prestimulus baseline. The N1 attenuation is presumably the result of a minimal arousal level, consistent with its gradual decrease at sleep onset (Ogilvie et al., 1991; Winter et al., 1995) and its small amplitude during Stage II–IV sleep (Campbell et al., 1992; Nielsen-Bohlman et al., 1991) and sufentanil anesthesia (Plourde et al., 1993). As described in the introduction, the N1 wave does not reflect a single underlying process. Both stimulus-specific and stimulus-nonspecific generators contribute to the scalp-recorded N1 (Näätänen and Picton, 1987). Motivation or attention may increase the action of the nonspecific generators, whereas drowsiness or sleep may decrease this nonspecific activity. Näätänen and Picton (1987) have interpreted these types of

changes in terms of arousal and modulation of sensory sensitivity. In line with this reasoning it is possible that propofol and/or alfentanil have particularly controlled the nonspecific generators of the N1. This suggestion is supported by studies in normals examining changes in the auditory N1 after intake of small doses of hypnotic drugs. For example, Wolpaw and Penry (1978) reported that ethanol decreased the amplitude of the vertex N1 wave but did not change the amplitude of the temporal T-complex. More recently, Pang and Fowler (1995) found that sub-anesthetic doses of nitrous oxide had a dose-dependent effect on the N1 evoked by the first stimulus in a brief train, whereas the N1 responses of the following stimuli remained unaffected. These results were taken as evidence that the non-specific N1 sub-component is particularly sensitive to drug-induced sedation. Furthermore, considering its presumed relationship with attention-triggering processes (Näätänen and Picton, 1987), the presence of such non-specific negativity may be a necessary condition for awareness. It therefore seems unlikely that in the current study the intraoperatively presented stimuli have reached consciousness. However, this does not exclude the possibility that the initial readout of sensory information and the formation of a sensory memory trace have remained (partly) unaffected by the administered anesthetic agents. Moreover, this latter suggestion is supported by the P1N1 and N1P2 amplitude differences found for the frequent and infrequent tones (see below). In other words, the current results leave the possibility that some implicit perception of auditorily presented stimuli may persist during anesthesia.

The nonspecific contribution to the N1 response may parallel the 'waking Processing Negativity (wPN)' described by Campbell et al. (1992). These authors suggested that a long duration negative wave (wPN) may overlap the awake ERP waveform. This negativity, occurring 25–200 ms after stimulus onset, is believed to be associated with attention mechanisms. Sleep may remove this negativity, causing N1 to be near baseline values and P1 and P2 to increase apparently in amplitude. A similar phenomenon may have occurred during general anesthesia and may have been responsible also for the induced changes in P1, N1 and P2 scalp distribution. According to these changes, the removed negativity should have had a frontal or frontocentral maximum. In addition, because the right hemisphere dominance of P1 and N1 increased during anesthesia, it may be hypothesized that the processes reflected in this non-specific negativity have differentially affected the activity of the right and left hemispheres.

In the present study evidence for differential processing in the awake state was found as a larger and seemingly prolonged N1 for the infrequent tones. Additionally, a sustained positivity following P2 was exclusively present after these stimuli. These effects may have resulted from the addition of a MMN and P3a respectively. However, the differences between the ERPs for frequent and infrequent tones were not very convincing, probably because the atten-

tion of the patients was very well distracted, due to our instruction and the fact that they were awaiting an important operation. Furthermore, inspection of the individual traces revealed that some patients showed predominantly an enlarged N1 whereas others showed mainly a small P3(a) response.

During anesthesia, P1N1 and N1P2 amplitudes were larger for frequent than for infrequent tones. This may imply a sustained ability to respond differently upon tones with different pitch and occurrence frequency. It remains to be addressed, however, whether these amplitude differences reflect genuine detection of stimulus deviance or whether they were due to selective refractoriness. With respect to N1, the first interpretation would assert that the N1 enlargement for infrequent tones may result from the addition of a MMN, reflecting the pre-perceptual detection of stimulus change (Näätänen and Picton, 1987). Arguments in favor of this interpretation are the presumed attention-independence of the MMN and the presence of a comparable process in the preoperative recordings. Additionally, the prominent overlap with the N1 deflection might be explained by the large difference in tone pitch employed in the current study, putting forward the onset of the MMN (Ford et al., 1976). Furthermore, a rather early onset of the MMN has also been reported during drowsiness (Winter et al., 1995), REM sleep and late Stage II sleep (Campbell et al., 1992), suggesting that a premature onset might be related to particular states of reduced arousal level. Moreover, in the study of Campbell et al. (1992) the claimed MMN seems even to start before onset of N1, which is in agreement with our results (Fig. 1c,d). For these reasons it is tempting to suggest that a small MMN might have been present during general anesthesia, although this seems in contrast with the widespread absence of a MMN during slow wave sleep, i.e. the sleep stage which is intuitively most comparable to anesthesia. This discrepancy might be explained by the different nature of these states and/or the variation in external (surgical) stimulation. Furthermore, it must be noted that we have recorded considerably more trials than that there are usually recorded in sleep studies, which may have had a beneficial effect on the ability to extract the small MMN component. However, some reserve is needed before ratifying this suggestion. After all, the alternative interpretation concerning differences in refractoriness effects for frequent and infrequent tones cannot be ruled out completely on the basis of our results. Further research is therefore needed to clarify the exact nature of the observed N1 amplitude differences.

During anesthesia also the P2 wave was found to be larger for the infrequent tones than for the frequent tones. The same phenomenon has been reported to be present during Stage II sleep (Harsh et al., 1994; Nielsen-Bohlman et al., 1991; Winter et al., 1995), but its origin and functional significance are unknown. Winter et al. (1995) considered it unlikely that the increase of this early positive peak would be equivalent to the P3a observed during wakefulness, but

they remained also indecisive whether it paralleled the awake P2. In contrast, Harsh et al. (1994) found no sufficient support in their data to exclude the possibility that the P2 increase may reflect the same process underlying the P3a in awake subjects. During sufentanil anesthesia Plourde et al. (1993) observed a fronto-central positivity for infrequent tones around 290 ms post-stimulus which they identified as a P3a. The claimed P3a was of small amplitude and showed considerable overlap with the preceding P2 deflection, but could be distinguished as a separate wave in at least some situations. From these descriptions it becomes apparent that the identity of the process underlying the increased positivity for infrequent stimuli remains as yet unidentified. However, it is important to note that during Stage II sleep the P2 increase for deviants has been found to be sensitive for the magnitude of stimulus deviance (Winter et al., 1995) and the type of instruction given (attend versus ignore) (Harsh et al., 1994). These results and the fact that a similar P2 effect could not be observed during the awake state suggest that the P2 increase for infrequent stimuli cannot solely be explained by differences in refractoriness. Consequently, it might be possible that some of the neural mechanisms underlying sensory discriminative processing remained active during anesthesia, at least in those patients for which a clear P2 difference could be observed.

Significant but low correlations were found between propofol plasma levels and P2 latency and between alfentanil plasma levels and P1 latency. Furthermore, propofol plasma levels were found to correlate with P1 and P1N1 amplitudes, but exclusively during CPB. Before CPB, propofol concentration correlated with P1 latency at Fz. Apparently, the relationship between anesthetic concentration and ERP parameters was not straight forward. Physiological processes involved in drug absorption, distribution, metabolism, and elimination may have all played a role in establishing the final effects of propofol and alfentanil. This is illustrated by the fact that dissimilar results were obtained during CPB, which is known to affect the above mentioned processes (Russell, 1991). In conclusion, ERP measures seem not to be reliable indicators of anesthetic plasma concentrations.

Nasopharyngeal temperature was found to affect all measured ERP amplitudes and latencies but the computed correlations were very low. This might be due to the slight or moderate cooling procedures employed during the operations, generating only a small variability in temperatures. Much higher correlations have been found between AEP brainstem components and nasopharyngeal temperature (Markand et al., 1984) and between AEP midlatency components and body temperature (Kileny et al., 1983). The observed effects in these studies were a progressively delay in peak latencies and more variable or reduced response amplitudes with decreasing temperatures. They were explained by the fact that hypothermia increases the action potential duration, reduces the nerve-conduction velocity and impairs synaptic transmission, producing a

slower, less effective neural activity. In the current study, P1 and P1N1 amplitudes showed also a reduction in amplitude with decreased temperatures. However, temperature effects on P1, N1 and P2 latency showed a reversed tendency as those reported for earlier AEP components. We have no sufficient explanation for this result, but it may have to do with the limitations of the peak-picking procedure.

Twenty-five percent of all recordings was judged to comprise a recognizable P1-N1-P2 complex. Most of these clear ERP responses were recorded before CPB suggesting that this period may be particularly critical with respect to the occurrence of auditory processing, presumably related to the high degree of surgical stimulation during this period. Furthermore, the relative high incidence of ERPs before CPB may account for the larger P1N1 and N1P2 amplitudes obtained during this period compared to those obtained during the other intraoperative recording periods. The number of patients showing no clear ERP response during any of the intraoperative recording periods is relatively small (30%). This contradicts the common opinion that auditory processing during anesthesia only rarely occurs. Furthermore, it justifies the search for intraoperative in addition to postoperative measures of information processing. The overall presence of ERPs appeared to be relatively independent of the anesthetic concentration or operation- and patient- characteristics. The presence of ERPs may depend on more subtle (neuro) physiological changes during the anesthesia period. Identification of measures reflecting these changes is important for clinical practice in order to derive early indicators for information processing which can be used for routine monitoring of anesthesia. This topic is being addressed in another study (De Beer et al., 1996).

In conclusion, this study has shown interesting similarities between early ERP responses recorded during sleep and anesthesia. This suggests possible parallels in the mechanisms underlying primary auditory processing during drug-induced and natural states of diminished arousal levels. Furthermore, it is suggested that recording of ERPs during anesthesia is valuable for clinical practice, providing a tool for demonstrating intraoperative perceptual processing at the moment that it might occur.

Acknowledgements

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