Midlatency auditory evoked potentials as indicators of perceptual processing during general anaesthesia


Summary

We tested the hypothesis that midlatency auditory evoked potentials (MLAEP) can predict the occurrence of long latency AEP components (LLAEP), which are taken as evidence for perceptual processing. Forty-one patients undergoing cardiac surgery were anaesthetized with propofol and alfentanil. During several periods of surgery we recorded LLAEP. Peak-to-peak amplitude measures were used to determine if a particular LLAEP recording trace contained a recognizable waveform. Both before and after each LLAEP recording epoch, MLAEP and the spontaneous electroencephalogram (EEG) were recorded. Peak latencies and amplitudes of brainstem peak V and midlatency peaks Na, Pa, Nb, Pb and Nc, characteristic frequencies from the spontaneous EEG, mean arterial pressure (MAP) and nasopharyngeal temperature (T) were compared between recording epochs with and without clear LLAEP waveforms. These variables were also used in a discriminant analysis to predict the occurrence of an LLAEP waveform. Pa and Nb latencies were significantly shorter both before and after recording epochs in which an LLAEP waveform occurred, compared with epochs in which no LLAEP waveform occurred. Using a combination of up to six EEG, MLAEP, MAP and T measures, it was possible to predict the occurrence or absence of an LLAEP waveform with a sensitivity of 89% and specificity of 86%. We conclude that MLAEP components provide information on the possibility of perceptual processing during general anaesthesia, and thus may be relevant for monitoring depth of anaesthesia. (Br. J. Anaesth. 1996; 77: 617–624)

Key words

Brain, evoked potentials. Monitoring, evoked potentials. Anaesthesia, depth.

Many studies on intraoperative memories suggest that auditory information processing may persist during general anaesthesia, but there is still no standardized method for determining during operation whether or not an auditory stimulus is actually perceived. The availability of such a method is an essential prerequisite for monitoring anaesthetic depth. Auditory evoked potentials (AEP) provide a method for monitoring the transmission and processing of auditory stimuli from the cochlea to the cortex. The AEP consists of a series of waves that are characterized by their latency (the time of occurrence after sound onset) and amplitude. Brainstem auditory evoked potentials (BAEP), consisting of waves I–VII, occur within 10 ms after stimulus presentation, and reflect activation of the acoustic nerve and brainstem auditory structures. Midlatency AEP components (MLAEP) occur between 10 and 100 ms after sound onset. MLAEP components are termed N0, P0, Na, Pa, Nb, Pb and Nc, and are thought to be generated in thalamic and cortical auditory structures. MLAEP components are followed by long latency AEP components (LLAEP) which reflect activation of the association areas of the cerebral cortex. LLAEP components P1, N1 and P2 reflect the more cognitive aspects of information processing. (No general agreement exists over the exact boundary to use between midlatency and long latency components. Theoretically, P1 and N1 are identical to Pb and Nc. In this article, labels P1 and N1 were used to indicate components elicited in an oddball paradigm, while labels Pb and Nc were used to indicate components elicited by clicks.)

Thornton has shown that BAEP components increase in latency with increased levels of volatile agents, whereas they remain unaffected by i.v. anaesthetics. Latency and amplitude of MLAEP components have been found to show dose-related changes with general anaesthetics that were highly similar for inhalation and i.v. agents. In addition, the decrease in Nb and Pb amplitude induced by anaesthesia was found to be reversed by surgical stimulation. These results suggest that MLAEP components are related to responsiveness of the auditory pathways. However, their occurrence is...
in sufficient evidence that the presented stimulus is actually perceived. The purpose of this study was to investigate the relationship between MLAEP components and auditory perception. Evidence of such a relationship would provide further support for the usefulness of the MLAEP for routine monitoring of perceptual processing during anaesthesia.

Previous research on this relationship has focused on the isolated forearm technique (IFT) and implicit memory. In a study by Thornton and colleagues, it was shown that responsiveness, as indicated by IFT, was associated with shorter latencies of MLAEP peak Nb. IFT measures the ability of a patient to respond to verbal commands during anaesthesia. Absence of a response may indicate unconsciousness, but it is also possible that the patient wanted to respond, but was unable. Furthermore, it may be difficult to distinguish general movements from a purposeful response to command. Another limitation is that this technique can only be used for a short period of time, to prevent ischaemia in the isolated arm. In a study by Schwender and co-workers, Pa latency was 100% sensitive and 77% specific in predicting implicit memory for material presented during the intraoperative period. Although this supports the notion that MLAEP measures reflect some degree of perceptual processing, the results of implicit memory tests are not determined exclusively by the effects of anaesthesia on perceptual processing but also on memory processes. In addition, the results of implicit memory tests may also be affected by intermediate processes between the time of stimulus administration and the time of testing.

To circumvent these disadvantages of the IFT and implicit memory tests, we focused on LLAEP components as a possible way of obtaining evidence for perceptual processing. The N1 and P2 components, occurring approximately 100 to 200 ms after a stimulus, are associated with early discrimination processes. Their amplitudes are influenced not only by the physical features of the stimuli, but also by the subject’s attention. The P3 component is a task-related component, most typically elicited by an infrequent stimulus presented against a background of frequent, standard stimuli (the so-called oddball task). This component, which has a latency of 250–600 ms, reflects controlled stimulus processing and target detection, presumably associated with conscious awareness of the presented stimulus. Evidently, recording of LLAEP components in addition to MLAEP components would create the possibility of relating early cortical MLAEP changes resulting from anaesthesia to variations in levels of perceptual and cognitive processing.

In this study, MLAEP and LLAEP were recorded during several periods of cardiac surgery with propofol–alfentanil anaesthesia. Our hypothesis was that MLAEP measures can predict the occurrence of LLAEP components (specifically the P1-N1-P2 complex), which is taken as the earliest evidence of perceptual processing. The predictive value of MLAEP measures was compared with that of mean arterial pressure, nasopharyngeal temperature and several spectral EEG measures.

Patients and methods

The study was performed at the Catharina Hospital, Eindhoven, and was approved by the local medical Ethics Committee. Informed consent was obtained from 41 patients (34 male) undergoing cardiac surgery. Mean age of the patients was 59 (range 38–74) yr. Two patients underwent aortic valve replacement and the others underwent coronary artery bypass grafting. Patients were premedicated approximately 2 h before surgery with morphine 10 mg s.c. Total i.v. anaesthesia was used with propofol and alfentanil. Anaesthesia was induced with a loading dose of propofol 2 mg kg⁻¹ and alfentanil 100 µg kg⁻¹, given over 12 min; after this, anaesthesia was continued with infusion rates of propofol of 8 mg kg⁻¹ h⁻¹ and alfentanil 4 µg kg⁻¹ min⁻¹ for 10 min, then propofol 6 mg kg⁻¹ h⁻¹ and alfentanil 3 µg kg⁻¹ min⁻¹ for 10 min and finally propofol 4 mg kg⁻¹ h⁻¹ and alfentanil 2 µg kg⁻¹ min⁻¹ for maintenance. Pancuronium 8 mg was used to facilitate tracheal intubation. Additional pancuronium 8 mg was given at the start of cardiopulmonary bypass (CPB). The lungs were ventilated mechanically with air and oxygen to maintain end-tidal carbon dioxide pressure at 4 kPa. Oxygen saturation was monitored continuously. Increases in arterial pressure were counteracted with nitroglycerin or ketamine and decreases with administration of i.v. fluids, calcium or inotropic drugs, together with reduced doses of propofol and alfentanil. During CPB moderate hypothermia to 32°C was used.

RECORDING PROCEDURE

Baseline recordings for both MLAEP and LLAEP were obtained on the morning of operation before patients were premedicated. During surgery MLAEP and LLAEP recordings were obtained during the following periods: before CPB (approximately 30 min after first incision); at the start of CPB; during CPB; at the end of CPB; and approximately 10 min after CPB.

In the event that surgery was too short to complete all recording series, period 3 was excluded. MLAEP and LLAEP were recorded successively during each of the above periods, as presented schematically in figure 1, because MLAEP components are typically evoked by presentation of auditory clicks, while LLAEP components are best elicited by tones with a much lower presentation rate. In addition, different filter settings are needed for these two types of AEP components, for which we used different EEG amplifiers. The total recording time in each recording period was limited to 22 min, as indicated in figure 1; typically it was about 15 min. The exact moment and duration of each recording epoch was dependent on the absence of disturbances caused by electrosurgery or the bypass pump.

An IBM-compatible 486 personal computer provided with a LabMaster analogue-to-digital (A/D) and digital-to-analogue (D/A) converter (Scientific Solutions, Solon OH) was used for presentation of MLAEP and LLAEP stimuli, control of the oddball task and acquisition of all neurophysiological signals, as described in the next sections.
LLAEP RECORDING AND PROCESSING

LLAEP were recorded during passive auditory odd-ball tasks. For baseline measurements, patients were instructed to ignore the stimuli. No specific instructions were given for the intraoperative recordings, because it was assumed that during anaesthesia patients would not be able to direct their attention towards any of the stimuli. Two tones of different pitch were presented binaurally through Nicolet Tip-10 insert earphones. The tones were 100-ms bursts of a digitally stored sine wave of 70 dB sound pressure level (SpL), with rise and fall times of 10 ms. Eighty percent of the stimuli were “standard” 1000-Hz tones, and 20% were “deviant” 2000-Hz tones. The inter-stimulus interval was 1044 ms. During two intraoperative oddball tasks (periods 1 and 4) five one-syllable words were presented repeatedly inter-mixed with the two types of tones. In these tasks the words had a probability of 0.15, compared with 0.70 for the standard tones and 0.15 for the deviant tones. After operation these words were tested for (covert) recognition, which will be reported in detail elsewhere (van Hooff and colleagues, in preparation). In the preoperative period, a total of 200 stimuli were presented. During surgery, 400–600 stimuli were presented because of a poorer signal-to-noise ratio.

For LLAEP processing, the raw electroencephalogram (EEG) was recorded from silver–silver chloride electrodes placed at Fz, Cz, Pz and two lateral positions C5 and C6, located midway between T3–C3 and T4–C4, respectively. Linked pre-auricular positions C5 and C6, located midway between T3–C3 and T4–C4, respectively. Linked pre-auricular points served as reference. Recording and averaging were performed as described previously, with the exception of filtering and artefact detection. In this study, the EEG signals were digitally filtered using a 33-point finite-impulse response bandpass filter with −3 dB cut-off frequencies of 2.7 and 8 Hz. The criteria for detecting an artefact were the occurrence of spikes greater than 110 µV, drift greater than 80 µV in a single trial or a difference in DC level in successive 250-ms epochs larger than 60 µV. The mean number of trials composing LLAEP in response to frequent tones, infrequent tones and words after artefact detection were 364 (SD 85), 87 (23) and 73 (14), respectively.

Peak amplitudes were determined for each individual waveform as being the most positive (for P1 and P2) and most negative (for N1) values in selected time windows based on the grand averages. P1 amplitudes were determined relative to the 200-ms pre-stimulus baseline, and N1 and P2 were determined with respect to their preceding peak (P1N1 and N1P2, respectively). P3 was not recognizable as a clear peak during anaesthesia and was therefore not quantified. Criteria for peak amplitudes were specified and used to judge whether or not a clear P1-N1-P2 complex could be distinguished in individual intraoperative recordings. Because LLAEP components were mostly clearly visible at Cz and because the recordings to frequent stimuli had the best signal-to-noise ratio, this was done for the Cz electrode position and the LLAEP to frequent tones only. When P1N1 and N1P2 amplitudes were larger than their median amplitudes (1.46 µV and 1.73 µV, respectively) and the correlation with an overall average waveform obtained by averaging all intraoperative LLAEP was larger than 0.55 (calculated over the first 800 ms of the response after tone-onset), then the recording was judged to be a clear LLAEP response, that is containing a recognizable P1-N1-P2 complex. The purpose of this assessment was to test if the presence of a clear LLAEP response could be predicted from the MLAEP.

MLAEP RECORDING AND PROCESSING

For MLAEP processing the raw EEG was recorded from Cz–A1 and Cz–A2, each referenced to Fpz. Recording and filtering of the EEG was performed as described previously. Clicks were delivered with random inter-stimulus intervals, according to a Poisson distribution, with an average stimulation rate of 80 clicks s⁻¹. An important implication of using this distribution for random presentation of stimuli is that the effects of interfering stimuli are distributed equally over the entire sweep, independent of sweep length. This results in a smoothing of the effect of interfering stimuli. We chose a sweep length of 270 ms for averaging of the MLAEP in this study to ensure that component Nc could be detected if present. Automatic detection of artefacts was used to exclude sweeps containing artefacts from the averaging process. The MLAEP was not used in further processing if, because of the occurrence of artefacts, the total number of sweeps in the resulting average was lower than 3000 (corresponding to a net recording time of 38 s). From the resulting averages the latency and amplitude of brainstem peak V and of midlatency peaks Na, Pa, Nb, Pb and Nc were determined. Brainstem peak V was used to check if a response was actually present: if peak V could not be determined, the entire MLAEP waveform was not used in further processing.

PROCESSING OF THE SPONTANEOUS EEG

The raw EEG recorded for MLAEP averaging was also used for spectral analysis, using the CCSA software package developed in our group. Before calculation of the spectra, the EEG was digitally
low-pass filtered, using a 69-point moving average filter with a $-3$ dB cut-off frequency of 32 Hz. Spectra were calculated from 8-s epochs using 2-s overlapping of epochs, and applying a Blackman time window to prevent spectral leakage. Detection and rejection of epochs from the filtered EEG that contained artefacts was done with the same algorithm as was used for detecting artefacts in the MLAEP. If the occurrence of artefacts caused the total number of remaining epochs for a specific recording to be lower than six (corresponding to a net recording time of 38 s), that recording was not used in further processing. The features derived from the calculated spectra were median frequency, 95% spectral edge frequency and peak power frequency, and percentage delta (0–4 Hz), theta (4–8 Hz), alpha (8–14 Hz) and beta (>14 Hz) power. The resulting spectral features for each recording were averaged so that one set of EEG features remained for each set of MLAEP features.

Because the raw EEG was high-pass filtered at 5 Hz to enhance the quality of the MLAEP recordings, the calculated spectral features are higher than values reported in the literature as being necessary for surgical anaesthesia,$^{16,17}$ especially for median and peak power frequency. Percentage delta power is lower in our study.

**RECORDING OF ARTERIAL PRESSURE AND TEMPERATURE**

The values of mean arterial pressure (MAP) and nasopharyngeal temperature ($T$) were measured at the start and end of each MLAEP recording epoch. To avoid large physiological changes during the recordings, limits of acceptability were defined for the changes in MAP and $T$. When the difference in MAP and $T$ values at the start and end of an MLAEP recording epoch exceeded the thresholds, as indicated in the first row of table 1, this MLAEP recording was excluded from further analysis. If neither MAP or $T$ exceeded these thresholds, then for each MLAEP recording the average of MAP and $T$ values obtained at the start and end of this recording epoch were calculated for inclusion in further analyses. When the differences in these average MAP and $T$ values for the MLAEP recordings before and after each LLAEP recording epoch exceeded the thresholds, as indicated in the second row of table 1, then this set of MLAEP and LLAEP recordings was excluded from further analysis. This criterion implies that sets of MLAEP and LLAEP recordings for which there were no MAP or $T$ values available, either before or after the LLAEP recording epoch, were also excluded from further analysis.

Systolic and diastolic arterial pressures were not included in the analysis, because during bypass no observations for these variables were available. Heart rate was also not included, partly because during CPB heart rate is zero, and partly because several patients were paced after CPB. This implies that heart rate contains no relevant information in these situations.

**STATISTICAL ANALYSIS**

MLAEP and EEG measures, MAP and $T$ (all recorded both before and after each LLAEP recording epoch) were tested for differences between recording epochs in which an LLAEP occurred and epochs in which no LLAEP occurred. We used Wilcoxon’s rank sum test for this comparison because of the low number of observations in the group consisting of recording epochs in which a reliable LLAEP occurred.

*Predicting the occurrence of an LLAEP*

Discriminant analysis was used to examine if it is possible to predict the occurrence of an LLAEP waveform in a specific recording epoch. Based on observations of MAP, $T$ and MLAEP, and EEG features, a discriminant function was estimated that optimally separates the group of recording epochs in which an LLAEP occurred from the group of recording epochs in which no LLAEP occurred. Estimation of the optimal discriminant function was performed several times, using different sets of features, to compare the predictive power of the various available features. First, it attempted to predict the occurrence of an LLAEP using only the observations for MAP and $T$ obtained at the start of each recording epoch. More variables were included for estimation of the discriminant function in subsequent analysis cycles. These added variables were the measures derived from the EEG (median, spectral edge and peak power frequency, and percentages of delta, theta, alpha and beta power) in the second cycle, the measures derived from the MLAEP (latencies and amplitudes of peaks V, Na, Pa, Nb, Pb and Nc) in the third cycle, and finally all MLAEP and EEG derived measures in the fourth cycle. These four cycles were repeated to include also the observations of the variables obtained at the end of each recording epoch.

In each cycle the discriminant analysis calculated the best linear combination of features from the total available data set by stepwise selection of variables. To prevent the resulting discriminant function from becoming difficult to interpret, we limited the number of variables to be included in the discriminant function to six in each cycle. The performance of the resulting discriminant function was tested after each cycle to see if its predictions agreed with the actual occurrence of an LLAEP waveform.

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**Table 1** Thresholds for mean arterial pressure (MAP) and nasopharyngeal temperature ($T$) for inclusion in the analysis. The threshold for changes in MAP was based on the maximally allowed range for MAP during CPB (40–70 mm Hg). The thresholds for changes in $T$ were based on a maximally allowed cooling and rewarming rate of 0.5°C min$^{-1}$.

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>$T$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal allowed difference between values obtained at start and end of MLAEP recording epoch</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Maximal allowed difference between values obtained before and after LLAEP recording epoch</td>
<td>30</td>
<td>5</td>
</tr>
</tbody>
</table>
Because in this study we had only a limited amount of data available, we used the leave-one-out method for cross validation. This implies that when we have \( n \) data points, the discriminant function was calculated from \( n - 1 \) data points and subsequently tested on the one remaining datum point. This was repeated \( n \) times so that each datum point was used once for testing. Performance was assessed in terms of sensitivity, specificity and accuracy. Sensitivity was defined as the fraction of epochs for which the occurrence of an LLAEP was predicted correctly by the discriminant function. Specificity was defined as the percentage of epochs for which the absence of an LLAEP was predicted correctly. Accuracy was defined as the percentage of epochs for which the occurrence or absence of an LLAEP was predicted correctly.

Results

In total, 176 LLAEP recordings were obtained during the 41 operations, of which 44 were judged as containing a clear LLAEP waveform (25%). Most of these clear LLAEP were recorded in the period before CPB, suggesting that perceptual processing occurred predominantly during this period. In Table 2 the total number of LLAEP recordings obtained during the various periods of surgery are summarized. Table 2 also summarizes the number of recordings in each period of surgery for which both before and after the recording epoch complete observations for MLAEP, EEG, MAP and \( T \) were available. Of these remaining recordings, nine recording epochs obtained in nine different patients contained a clear LLAEP.

Examples of baseline and intraoperative LLAEP waveforms are presented in figure 2. Compared with preoperative LLAEP, intraoperative recordings were delayed and more positive going. N1, typical of preoperative recordings, decreased to or below pre-stimulus baseline levels during anaesthesia. A P3 response was generally absent in individual LLAEP traces. A more detailed description of the LLAEP results is presented elsewhere (van Hooff and colleagues, submitted). Examples of baseline and intraoperative MLAEP waveforms are presented in figure 3. Compared with baseline MLAEP waveforms, intraoperative MLAEP recordings showed longer latencies and smaller amplitudes. Compared with baseline EEG measures, intraoperative EEG

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**Table 2** Number of LLAEP recordings during the various periods of surgery. After selection=number of LLAEP recordings remaining after selecting those recordings for which both before and after the recording epoch, observations for MAP, \( T \), MLAEP and EEG measures were present.

<table>
<thead>
<tr>
<th>No. recordings</th>
<th>After selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>176 44</td>
</tr>
<tr>
<td>Before CPB</td>
<td>35 19</td>
</tr>
<tr>
<td>At start of CPB</td>
<td>34 6</td>
</tr>
<tr>
<td>During CPB</td>
<td>33 —</td>
</tr>
<tr>
<td>At the end of CPB</td>
<td>34 11</td>
</tr>
<tr>
<td>After CPB</td>
<td>40 8</td>
</tr>
</tbody>
</table>

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**Figure 2** Examples of baseline (left) and intraoperative (right) LLAEP waveforms. Solid lines = responses to frequent stimuli, broken lines = responses to infrequent stimuli. Negativity is plotted upwards by convention.

**Figure 3** Examples of baseline (left) and intraoperative (right) MLAEP waveforms. Scaling of the axes is different from figure 2.
measures showed a decrease in median, spectral edge and peak power frequencies, an increase in percentage delta and theta power, and a decrease in percentage beta power.

Mean (±SD) values for MLAEP and EEG features, mean arterial pressure (MAP) and nasopharyngeal temperature (T) obtained before and after LLAEP recording epochs are presented in figure 4. Latencies of MLAEP peaks Pa and Nb were significantly shorter (P < 0.050 and P < 0.045, respectively) at the start of LLAEP recording epochs in which a clear LLAEP occurred, compared with recording epochs in which no clear LLAEP occurred. Latency of MLAEP peak Pa was significantly shorter (P = 0.020) at the end of LLAEP recording epochs in which a clear LLAEP occurred, compared with recording epochs in which no clear LLAEP occurred. Mean arterial pressure was significantly higher (P = 0.042) at the end of LLAEP recording epochs in which a clear LLAEP occurred, compared with recording epochs in which no clear LLAEP occurred.

The variables used in the discriminant function and its performance in predicting the occurrence of an LLAEP are summarized in Table 3. Adding only EEG features to the discriminant function did not improve the performance of the discriminant function beyond the performance of using only mean arterial pressure. Adding features from the MLAEP to the discriminant function improved specificity.
that is correct prediction of absence of an LLAEP waveform. Adding features from both the MLAEP and EEG improved sensitivity and specificity. Using MLAEP and EEG measures obtained both at the start and end of LLAEP recording epochs mainly improved sensitivity, that is correct prediction of the presence of an LLAEP waveform compared with using only variables obtained at the start of LLAEP recording periods.

Discussion

The hypothesis underlying this study was that MLAEP measures can predict the occurrence of LLAEP components during general anaesthesia. Our basic assumption was that the occurrence of LLAEP components can be taken as the earliest evidence for perceptual processing. It has been demonstrated that the N1 and P2 components reflect some level of perception and that P3 reflects controlled stimulus processing and target detection. These LLAEP components have in common that they are sensitive to the subject’s psychological state, that is their amplitude and latency vary with attention, sleep or anaesthesia. A study by Jessop and colleagues showed a correlation between amnesia and presence or absence of P3.

When using an inter-stimulus interval of 1 s, and presenting a minimum of 200 stimuli (160 frequent and 40 infrequent stimuli), LLAEP recording during anaesthesia would require at least 3 min. Therefore, LLAEP themselves cannot be used for monitoring purposes, because rapid fluctuations in anaesthetic state cannot be detected. Instead, LLAEP can be used as a reference measure, providing information on whether or not auditory information processing actually occurs. If measures more suitable for monitoring, such as MLAEP components or spectral EEG measures, were to appear to be predictive with respect to the occurrence of LLAEP, this would be strong evidence for the use of these measures. It has been suggested that recording of MLAEP components also has the drawback that a relatively long acquisition time is needed. A study by van de Velde, Cluitmans and Declerck showed, however, that using random presentation of auditory stimuli, as was used in this study, may result in the acquisition of acceptable MLAEP waveforms within 40–60 s.

Table 3 Performance in terms of sensitivity, specificity and accuracy of different combinations of types of measured variables to predict the occurrence of an LLAEP. The first column indicates the group of variables available to the discriminant analysis, the second column indicates which of these variables were actually selected, in order of importance.

<table>
<thead>
<tr>
<th>Variable group</th>
<th>Variables used in discriminant function</th>
<th>Sens. (%)</th>
<th>Spec. (%)</th>
<th>Acc. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtained before LLAEP recording epoch</td>
<td>MAP + T</td>
<td>67</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>MAP + T + EEG</td>
<td>67</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>MAP + T + MLAEP</td>
<td>Lat Nb, MAP, amp V, amp Pb, amp Nc</td>
<td>67</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>MAP + T + MLAEP + EEG</td>
<td>Lat Nb, beta, amp Nc, amp V, MAP, sef</td>
<td>78</td>
<td>84</td>
</tr>
<tr>
<td>Obtained before (b) or after (a) LLAEP recording epoch</td>
<td>MAP + T</td>
<td>56</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>MAP (a)</td>
<td>56</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>MAP + T + EEG</td>
<td>Lat Pa (a), amp Nc (b), MAP (a), amp V (b), amp V (a), lat V (b)</td>
<td>78</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>MAP + T + MLAEP</td>
<td>Lat Pa (a), beta (b), amp V (b) amp V (a), amp Nc (b), sef (b)</td>
<td>89</td>
<td>86</td>
</tr>
</tbody>
</table>

OCCURRENCE OF LLAEP WAVEFORMS

In agreement with our previous study, P3 was not observed in individual intraoperative recordings, indicating that it is not likely that patients had awareness for the stimuli. Anaesthetic concentrations of fentanyl–isoflurane also suppressed the occurrence of a P3 response. To date, only Plourde and colleagues claimed to have observed a P3 sub-component (P3a) during some periods of cardiac surgery during sufentanil anaesthesia. Although P3 is promoted frequently as being a promising measure to detect intraoperative awareness, it seems too easily abolished by surgical anaesthesia. Therefore, the presence of earlier LLAEP components, reflecting early perceptual processes (presumably automatically), was taken as a reference measure in this study. A clear P1-N1-P2 complex was present in 25% of intraoperative recordings. At first sight, this seems only a small proportion of all intraoperative recordings. However, these clear LLAEP were recorded in 28 of 41 patients, indicating that in 68% of all patients auditory processing persisted during some period of surgery.

Unfortunately, not all LLAEP obtained were preceded and followed by MLAEP and EEG recordings within the imposed time limit of 90 s. This was because of the restrictions imposed by external disturbances (e.g. electro-surgery), sudden changes during operation (e.g. onset of CPB) and anaesthetic or surgical intervention (e.g. defibrillation). Additionally, considerable effort was made to avoid large physiological changes during each series of recordings. After application of criteria to ensure the continuity of nasopharyngeal temperature and mean arterial pressure, 52 recording epochs, each comprising a series of MLAEP, LLAEP and MLAEP recordings as indicated in figure 1, remained for further analysis. From these 52 recordings, nine were judged as containing a clear LLAEP waveform (17%).

PREDICTIVE VALUE OF MLAEP AND EEG MEASURES

Pa and Nb latencies were shorter and MAP was higher when they were recorded close to LLAEP
recording epochs comprising a clear LLAEP waveform than when they were recorded close to LLAEP recording epochs comprising no reliable LLAEP waveform (see fig. 4). This suggests a possible relationship between these measures and the presence of LLAEP components, that is the ability of higher level processing. This suggestion is supported by earlier observations of Thornton and colleagues and Schwender and colleagues, as described above. The predictive quality of Pa and Nb latencies in addition to MAP can further be derived from the fact that one or the other was always selected first in the discriminant functions. Because both variables are highly correlated they were not selected simultaneously by the discriminant analysis. MLAEP amplitudes, spectral EEG measures and nasopharyngeal temperature were not significantly different, whether or not the nearby LLAEP recording epochs comprised a clear LLAEP waveform. Nevertheless, discriminant analysis revealed that some of these variables in combination had predictive value with respect to the occurrence of clear LLAEP waveforms.

The results of our study indicate that both MLAEP and EEG measures may be used for predicting the occurrence of perceptual processing during anaesthesia. We found an accuracy of 87% in predicting the occurrence of an LLAEP waveform within a limited period of time, using MLAEP and EEG measures obtained at the start and end of that period of time. Accuracy was still 83% when only data obtained before the actual occurrence of an LLAEP waveform were used for this prediction.

In summary, we used LLAEP components for assessment of perceptual processing. The advantages of this technique are that it may also be used during longer periods of surgery, and that perceptual processing is assessed at the time it occurs. However, the long acquisition time needed for obtaining the LLAEP makes it unsuitable for routine monitoring. The results of our study provide additional support for the notion that the MLAEP and (to a lesser extent) the EEG may be used for routine monitoring of perceptual processing during anaesthesia. This may improve the conventional assessment of the risk of awareness based on clinical signs such as arterial pressure and heart rate.

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