CLINICAL INVESTIGATIONS

Anesthesiology
80:493–501, 1994

J. B. Lippincott Company, Philadelphia

# Midlatency Auditory Evoked Potentials and Explicit and Implicit Memory in Patients Undergoing Cardiac Surgery

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*Background:* A high incidence of intraoperative awareness during cardiac surgery has been reported. Midlatency auditory evoked potentials (MLAEP) have been used recently as an indicator of awareness. In the current study, memory for information presented during anesthesia was investigated using MLAEP as one experimental indicator in 45 patients scheduled for elective cardiac surgery.

*Methods:* In all patients general anesthesia was maintained using high-dosage fentanyl (1.2 $mg \cdot h^{-1}$). In addition, the patients of group 1 (n = 10) received flunitrazepam (1.2 $mg \cdot h^{-1}$), the patients of group 2 (n = 10) isoflurane (0.6–1.2 vol%), and the patients of group 3 (n = 10) propofol (4–8 $mg \cdot kg^{-1} \cdot h^{-1}$). Group 4 (n = 15) served as a control, and those patients were assigned randomly to one of the anesthetic regimes. After sternotomy and before cardiopulmonary bypass, an audiotape, which included an implicit memory task, was presented to the patients of groups 1–3. Auditory evoked potentials were recorded while the patients were awake and during general anesthesia immediately before and after the audiotape presentation. Latencies of the brain stem peak V and the early cortical potentials Na and Pa were measured.

*Results:* Three to 5 days postoperatively no patient had a clear explicit memory of intraoperative events. However, there were statistically significant differences in the incidence of implicit recall among the groups. Five patients in the flunitrazepam–fentanyl group, 1 patient in the isoflurane–fentanyl group, 1 patient in the propofol–fentanyl group, and no patient in the control group showed an implicit memory of the intraoperative tape message. In the awake state, MLAEP showed high peak-to-peak amplitudes and a periodic waveform. In the patients with implicit memory postoperatively, MLAEP continued to show this pattern during general anesthesia. The early cortical potentials Na and Pa did not increase in latency or decrease in amplitude before or after the audiotape presentation. In contrast, in the patients without implicit memory, MLAEP waveform was severely attenuated or abolished. Na and Pa showed marked increases in latencies and decreases in amplitudes or were completely suppressed. In 9 patients, including all patients (7 of 9) with implicit memory, Pa latency increased less than 12 ms, and 21 of 23 patients without implicit memory showed a Pa latency increase of greater than 12 ms during anesthesia and the audiotape presentation. Therefore, the Pa latency increase of greater or less than 12 ms may provide sensitivity of 100% and specificity of 77% in distinguishing patients with implicit memory from patients without implicit memory postoperatively.

*Conclusions:* When the early cortical potentials of MLAEP are preserved during general anesthesia, auditory information may be processed and remembered postoperatively by an implicit memory task. (Key words: Anesthetics, intravenous: fentanyl; flunitrazepam; propofol. Anesthetics, volatile: isoflurane. Surgery: cardiac. Memory: explicit; implicit. Monitoring: auditory evoked potentials.)

CASE reports and clinical studies about intraoperative awareness differ considerably, presumably because of different patient populations, anesthetic techniques, and methods of monitoring and defining awareness. Despite these differences, all reports point out that auditory stimuli in particular can be perceived intraoperatively and recalled postoperatively. This suggests that the auditory modality is apparently the most receptive sensory channel for perception during general anesthesia.[1–5]

The process of transduction, transmission, and processing of acoustic stimuli from the cochlea to the cortex can be monitored by recording auditory evoked potentials (AEP).[6] Early components of the AEP are generated mainly in the brain stem (brain stem auditory evoked potentials [BAEP], 0–10 ms poststimulus) and represent the process of stimulus transduction and early transmission.[6] The midlatency auditory evoked potentials (MLAEP) are observed 10–100 ms after stimulus presentation, and they are generated within cortical regions of the auditory system.[6–10] The late auditory evoked potentials reflect neural activity of association

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Received from Ludwig-Maximilians-University, Munich, Germany. Accepted for publication September 23, 1993.

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areas 100–1,000 ms after stimulus onset. They are strongly influenced by stimulus evaluation and cognitive analysis.[11–14] The early auditory evoked potentials, generated in the brain stem, are minimally affected by general anesthetics and therefore cannot be used to monitor auditory information processing during general anesthesia.[15–17] The late cortical components show considerable variation in latency and amplitude during the awake state.[6,11] In contrast, midlatency peaks of the AEP show little variability. During general anesthesia with one of a number of general anesthetic agents, MLAEP are suppressed in a dose-dependent manner.[15–18] Recording of MLAEP may therefore offer an opportunity to monitor auditory information processing in the primary auditory cortex during general anesthesia.

A necessary condition for the retrieval of information perceived intraoperatively is the presence of a memory system that is at least partially unimpaired. New experimental evidence suggests a difference between implicit and explicit memory functions. Explicit memory requires the conscious recollection of a previous episode, including the spatiotemporal context in which the event occurs, and the self as the experiencer of the event. Implicit memory is revealed by a change in task performance that is attributable to information acquired during such an episode and is expressed without any conscious or deliberate recollection of the experience.[19–21] Until now, it has been far from clear which type and which dose of the commonly used anesthetic agents reliably suppress auditory stimulus processing, conscious and subconscious perceptions, encoding, and explicit and implicit recall of auditory stimuli.

A high incidence of intraoperative awareness and postoperative recall of intraoperative events can be observed in patients undergoing cardiac surgery.[22,23] The aim of the current study was to investigate implicit and explicit memory in patients undergoing cardiac surgery. For the maintenance of anesthesia, high-dose opioid analgesia was used, combined with a benzodiazepine, isoflurane, or propofol. The main goals of this study were to determine whether explicit or implicit memory is present during cardiac surgery, and if so, whether memory functions can be related to specific characteristics of MLAEP.

## Materials and Methods

Institutional ethics committee approval was granted, and informed consent was obtained from 45 patients scheduled for elective cardiac surgery. All patients were to undergo open-chest surgery, *i.e.*, aortocoronary bypass grafting or valve replacement. In all patients, hypothermic cardiopulmonary bypass was used. Only patients who had clinically normal hearing levels and who could write, read, and speak the German language fluently were included. The perioperative psychological care of the patients included a short preoperative visit, the preparation of an intraoperative audiotape, and a postoperative interview, all of which were performed by the same investigator (AK). The day before surgery, this investigator introduced herself to the patients to establish rapport and to achieve the patient's cooperation. She told the patients that she would accompany them throughout the perioperative period, giving some short, positive suggestions for the perioperative course.

All patients received a benzodiazepine (flunitrazepam 1–2 mg orally) 45–60 min before anesthesia. Then, patients were assigned randomly to one of four patient groups. Anesthesia was induced in group 1 (n = 10) with flunitrazepam and fentanyl (0.01 and 0.01 $mg \cdot kg^{-1}$, respectively) and in group 2 (n = 10) and 3 (n = 10) with etomidate and fentanyl (0.25 $mg \cdot kg^{-1}$ and 0.005 $mg \cdot kg^{-1}$, respectively). For maintenance of anesthesia all patients received high-dose fentanyl analgesia (1.2 $mg \cdot h^{-1}$). In addition, the patients of group 1 received flunitrazepam (1.2 $mg \cdot h^{-1}$), the patients of group 2 isoflurane (0.6–1.2 vol%), and those of group 3 propofol (4–8 $mg \cdot kg^{-1} \cdot h^{-1}$) to maintain general anesthesia. For muscle relaxation, pancuronium 0.1 $mg \cdot kg^{-1}$ was given. The patients of group 4 (n = 15) were randomly assigned to one of the three anesthetic regimes.

A three-lead electrocardiogram, heart rate, systolic and diastolic arterial blood pressures *via* an 18-G catheter in the radial artery, and central venous pressure *via* a 14-G central venous catheter placed *via* the internal jugular vein were recorded continuously. Mean arterial pressure was maintained at greater than 80 mmHg. Body core temperature was measured by an esophageal temperature probe and maintained at 34.5°C in the prebypass period using heated blankets and warmed infusions. Patients' lungs were mechanically ventilated with a 1:1 mixture of oxygen and nitrous oxide to achieve an arterial carbon dioxide tension of 35–40 mmHg, as verified by intermittent arterial blood gas analysis. Group 4 served as a control, and patients were not exposed to the audiotape.

After sternotomy, but before cardiopulmonary bypass, an audiotape, which included an implicit memory task, was presented to the patients of groups 1–3. The tape's duration was approximately 10 min. The text contained positive and supportive suggestions for postoperative recovery. In this instance a short version of the novel *Robinson Crusoe* was told. It provided an example of how a person overcame a very difficult situation. The story was meant to be a parable for the patients to cope with their current difficult situation and facilitate postoperative recovery. The parable illustrated that intellectual knowledge (Robinson Crusoe) and unconscious skill (Friday) can form a symbiosis to master encountered difficulties. The story was only told once; "Robinson Crusoe" was mentioned four times; and at the end of the text the patients received the suggestion to associate "Robinson Crusoe" when they were asked about their associations to "Friday" 3–5 days after the operation.

Explicit and implicit memory were tested in a postoperative interview of approximately 30 min. First, the patients were invited to talk about their experience during anesthesia and surgery and the intensive care unit period, with regard, for instance, to pain, mood, and well-being. Then patients were asked to remember explicitly anything they may have perceived during anesthesia. To test implicit memory the patients were invited to name any spontaneous association ("the first word that comes to mind") with the code word "Friday" (*i.e.*, the key word "Robinson Crusoe"). No emphasis was put on the question, in attempt to hide that this was a special aspect of the interview. Implicit recall was tested roughly in the middle of the talk so that the patients had approximately 15 min to form their associations. Finally, at the end of the interview the patients were asked if anything remained that they wanted to talk about, and anything else that they may have associated with the code word "Friday." The interview was closed with some short, positive suggestions for the postoperative recovery. All experimental evaluations were conducted under double-blind conditions: neither the patients nor the interviewer knew which anesthetic had been used or whether an audiotape had been presented.

AEP were recorded while patients were awake and during general anesthesia immediately before and immediately after the audiotape presentation. The electrodiagnostic system Pathfinder I (Nicolet Instruments) was used for auditory stimulation, registration, and analysis of evoked potentials. Rarefaction clicks of 0.1 ms at 70 dB above the normal hearing level were presented binaurally with a stimulation frequency of 9.3 Hz using acoustically shielded earphones (TDH 39, Amplivox, Manchester, England). For recording, silver electrodes were positioned at Cz and $A_1/A_2$ with Fpz as ground (according to the international 10–20 system). The impedance of all electrodes was less than 2.0 kohm. An epoch of 100 ms (bin width 0.2 ms) was bandpass-filtered (1–1,500 Hz) with an analogue Butterworth filter (roll-off 6 dB/octave) and averaged across 1,000 stimulus presentations. The recording procedure was controlled visually on a monitor, and an automatic artifact detector rejected signals greater than 96% of full scale. To guarantee reliability of the signal and correct transduction and transmission of the auditory stimuli, evoked potentials without a brain stem response (peak V) also were rejected. For off-line data analysis, latencies of the peaks V, Na, Pa, Nb, P1, and N1 were measured. For frequency analysis a fast-Fourier transformation was used to calculate power spectra of the MLAEP.

For a statistical comparison of the latencies of peaks V, Na, and Pa, the Wilcoxon test was used within groups and the Kruskal-Wallis test between groups. The incidence of implicit memories was compared between groups using the chi-squared test. $\alpha < 5\%$ ($P < 0.05$) was considered statistically significant. Statistical analysis included Bonferroni's correction ($\alpha$ adjustment) to account for multiple comparisons. Sensitivity and specificity were calculated for the relation between the change of Pa latency and the incidence of implicit memory.

## Results

The four groups were comparable in terms of age, sex, weight, height, ASA physical status, type and dose of premedication, type of surgery, total time of surgery and anesthesia, total time of cardiopulmonary bypass and aortic occlusion, lowest temperature during cardiopulmonary bypass, temperature during separation from cardiopulmonary bypass, and intraoperative changes of hemodynamic data (table 1).

In the postoperative interview none of the patients was able to recollect explicit memories of intraoperative events. Some patients stated having heard voices or noise, but these perceptions could not be related definitively to the intraoperative situation. Typical associations to the code word "Friday" were "approaching weekend," "last working day of the week," or "fish for lunch or dinner." After these statements some patients spontaneously associated "Robinson Crusoe." Typical reproductions of the story of Robinson Crusoe

**Table 1. Demographic and Intraoperative Hemodynamic Data of the Four Groups**

| | Group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | | 2 | | 3 | | 4 | |
| Number of patients (n) | 10 | | 10 | | 10 | | 15 | |
| Age (yr) (x ± SD) | 57.4 | 8.6 | 61.6 | 5.2 | 61.2 | 5.8 | 56.8 | 8.1 |
| Sex (male/female) (n) | 8 | 2 | 8 | 2 | 7 | 3 | 12 | 3 |
| Weight (kg) (x ± SD) | 73.5 | 8.0 | 76.0 | 10.5 | 67.6 | 11.0 | 71.6 | 10.1 |
| Height (cm) (x ± SD) | 170 | 8.8 | 172 | 5.3 | 168 | 6.0 | 170 | 10.5 |
| ASA physical status (x ± SD) | 2.40 | 0.5 | 2.63 | 0.5 | 2.64 | 0.5 | 2.30 | 0.5 |
| Premedication: flunitrazepam [mg] (x ± SD) | 2.00 | | 2.00 | | 1.91 | 0.3 | 2.00 | |
| Type of surgery (n) | | | | | | | | |
| CABG | 7 | | 5 | | 5 | | 10 | |
| CABG + AR | 2 | | 1 | | 1 | | 2 | |
| AVR | 1 | | 2 | | 2 | | 2 | |
| MVR | 0 | | 0 | | 2 | | 0 | |
| AVR + MVR | 0 | | 2 | | 0 | | 1 | |
| Type and dose of anesthesia | | | | | | | | |
| Flunitrazepam (1.2 mg/h) + Fentanyl (1.2 mg/h) (n) | 10 | | | | | | 5 | |
| Isoflurane (0.6–1.2 vol%) + Fentanyl (1.2 mg/h) (n) | | | 10 | | | | 5 | |
| Propofol (4–8 $mg/kg^{-1} \cdot h^{-1}$) + Fentanyl (1.2 mg/h) (n) | | | | | 10 | | 5 | |
| | x | ±SD | x | ±SD | x | ±SD | x | ±SD |
| Total time of (tt) surgery (min) | 207.5 | 37.4 | 172.5 | 46.8 | 195.5 | 30.2 | 208.5 | 47.6 |
| tt anesthesia (min) | 268.5 | 45.7 | 216.3 | 54.0 | 235.5 | 41.3 | 258.4 | 58.2 |
| tt CPB (min) | 85.0 | 14.1 | 79.4 | 56.3 | 71.4 | 19.6 | 88.5 | 46.5 |
| tt aortic occlusion (min) | 55.0 | 13.5 | 51.3 | 34.3 | 42.9 | 13.7 | 57.0 | 29.3 |
| Lowest temperature during CPB (° C) | 28.5 | 1.2 | 29.1 | 1.5 | 28.1 | 0.8 | 27.6 | 1.4 |
| Temperature at end of CPB (° C) | 36.7 | 0.2 | 36.3 | 0.4 | 36.4 | 0.5 | 36.4 | 0.4 |
| HR awake ($min^{-1}$) | 63.0 | 7.1 | 61.9 | 10.0 | 64.3 | 12.7 | 69.0 | 12.0 |
| HR after induction | 63.8 | 7.7 | 60.6 | 14.5 | 58.3 | 7.2 | 70.5 | 14.4 |
| HR after skin incision | 63.5 | 8.2 | 66.3 | 11.9 | 61.7 | 10.0 | 68.5 | 12.5 |
| HR after sternotomy | 75.7 | 16.6 | 69.4 | 9.4 | 71.5 | 11.5 | 72.0 | 12.3 |
| HR after CPB | 92.1 | 10.5 | 93.1 | 13.3 | 89.6 | 23.3 | 99.5 | 9.0 |
| HR end of surgery | 95.9 | 11.4 | 93.8 | 11.6 | 93.0 | 21.3 | 97.5 | 8.9 |
| SAP awake (mmHg) | 126 | 13.1 | 123 | 14.9 | 124 | 20.4 | 127 | 18.9 |
| SAP after induction | 122 | 12.3 | 121 | 14.6 | 107 | 18.0 | 123 | 15.7 |
| SAP after skin incision | 117 | 16.5 | 126 | 5.2 | 123 | 22.8 | 131 | 19.8 |
| SAP after sternotomy | 132 | 17.4 | 130 | 8.9 | 114 | 16.7 | 125 | 7.6 |
| SAP after CPB | 115 | 15.1 | 119 | 9.9 | 109 | 17.7 | 119 | 12.2 |
| SAP end of surgery | 122 | 14.9 | 125 | 9.3 | 110 | 13.9 | 113 | 19.9 |
| DAP awak (mmHg) | 72.0 | 7.5 | 69.4 | 10.2 | 72.6 | 11.0 | 73.0 | 6.7 |
| DAP after induction | 70.0 | 7.1 | 71.3 | 8.3 | 60.0 | 7.4 | 68.0 | 6.3 |
| DAP after skin incision | 64.5 | 4.4 | 72.5 | 4.6 | 67.9 | 13.7 | 72.0 | 7.9 |
| DAP after sternotomy | 72.5 | 9.8 | 73.8 | 7.4 | 63.3 | 11.8 | 70.0 | 8.2 |
| DAP after CPB | 62.5 | 6.8 | 66.9 | 4.6 | 62.2 | 3.7 | 66.0 | 8.4 |
| DAP end of surgery | 66.5 | 6.3 | 68.8 | 3.5 | 63.8 | 5.3 | 65.0 | 12.7 |

CABG = coronary artery bypass grafting; AVR = aortic valve replacemernt; MVR = mitral valve replacement; CPB = cardiopulmonary bypass; HR = heart rate; SAP = systolic arterial blood pressure; DAP = diastolic arterial blood pressure.

were as follows: "When you say 'Friday,' I think of an island and the story of Robinson Crusoe, but I think this has nothing to do with your question." Another typical answer was: "When you say 'Friday,' I remember that when I was a child we used to play on a little island in a river near my parent's home. We called that place Robinson island." It is noteworthy that all patients with implicit memory for "Robinson Crusoe" denied that their associations were related to something heard during anesthesia.

The incidence of implicit memory was different among the four groups. No patient in the control group (group 4), the patients who did not hear the audiotape intraoperatively, associated the key word ("Robinson Crusoe") with the code word ("Friday"). In contrast, five patients of group 1, one patient of group 2, and one patient of group 3 showed implicit memory for the intraoperative tape message. Implicit recall was statistically significant more often in group 1 than in the control group (group 4) or group 2 or group 3 ($P < 0.01$).

Figure 1 shows an original tracing of an AEP (left) and its power spectrum (right) of an awake patient. The Roman numeral V indicates BAEP, giving evidence that auditory stimuli were transduced and transmitted.[6] Na, Pa, Nb, and P1 (MLAEP) are generated mainly in the primary auditory cortex of the temporal lobe,[6–9] and they are the electrophysiologic correlate of the primary cortical processing of auditory stimuli. The MLAEP shows large peak-to-peak amplitudes and a characteristic periodic waveform, and the power spectrum has its maximal energy in the 30–40-Hz frequency range.

Original tracings of the MLAEP of two patients without implicit memory are presented in figures 2A and 2B. In every top trace one can see the AEP of the awake patients. The BAEP can be easily identified. The MLAEP show high amplitudes and their characteristic periodic waveform. During general anesthesia in these patients, BAEP could be identified as in the awake state. In contrast, during anesthesia, MLAEP showed markedly increased latencies and decreased amplitudes, or they were completely suppressed.

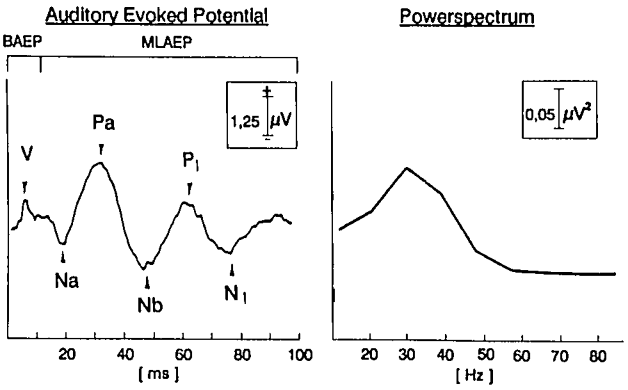


**Fig. 1. Original tracing of an auditory evoked potential (*left*) and its power spectrum (*right*) of an awake patient. V = the brain stem auditory evoked response (BAEP); Na, Pa, Nb, and P1 = the midlatency auditory evoked potentials (MLAEP).**

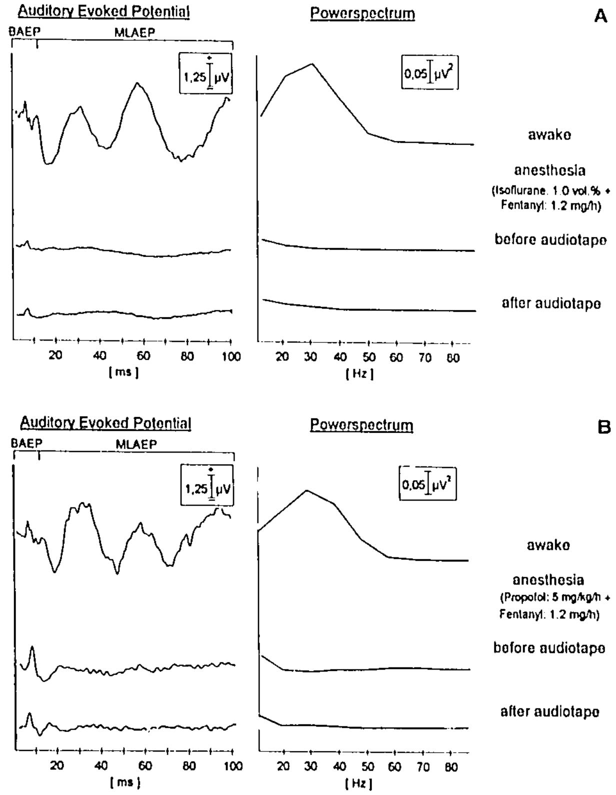


**Fig. 2. (*A* and *B*) Original tracings of the auditory evoked potentials of two patients without implicit memory. In those of the awake patients (all top traces), brain stem auditory evoked potentials can be identified easily. Midlatency auditory evoked potentials show high amplitudes and a characteristic periodic waveform. During general anesthesia, before and after the audiotape presentation (every second and third trace) in these patients, brain stem auditory evoked potentials can be identified as in the awake state, whereas the midlatency auditory evoked potential waveform is severely attenuated or abolished.**

A different picture was seen in the AEP of the two patients, presented in figures 3A and 3B. These patients could remember "Robinson Crusoe" implicitly after the operation. The MLAEP of the awake patients are again characterized by high amplitudes and a periodic waveform. During general anesthesia before and after the audiotape was presented to these patients, BAEP as well as MLAEP were similar to those of the awake state. The high amplitudes and periodic waveforms of the early cortical potentials suggest a preservation of cortical processing of auditory information in these patients.

Table 2 presents mean values and standard deviations of latencies of the peaks V, Na, and Pa (in milliseconds) for the patients with and without implicit memory. La-

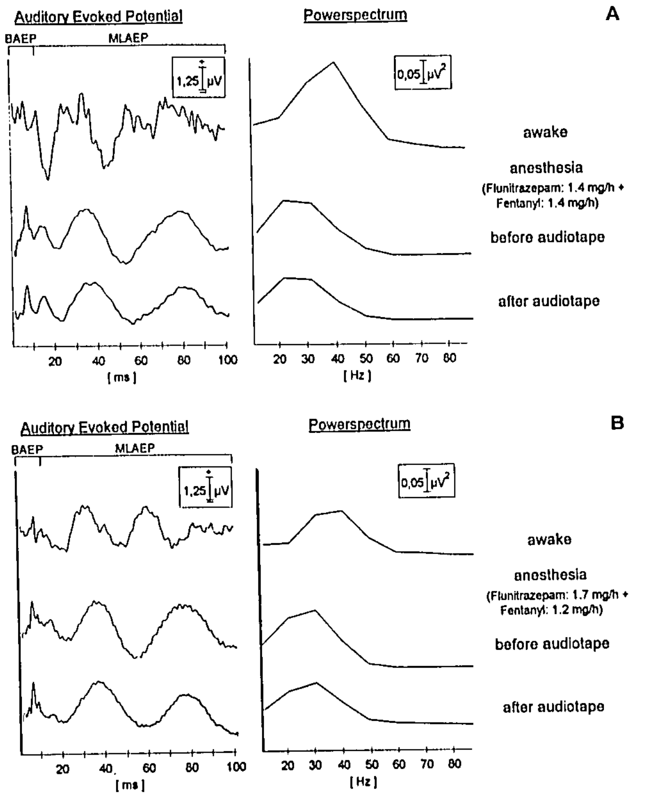


**Fig. 3. (*A* and *B*) Auditory evoked potentials of two patients who could remember "Robinson Crusoe" implicitly after the operation. Those of the awake patients are characterized by high amplitudes and a periodic waveform and continue to show this pattern during general anesthesia.**

tencies of the peaks Na and Pa are significantly prolonged in the patients without implicit memory compared to the awake patients or the patients with implicit memory postoperatively. In the patients with implicit memory, Na and Pa latencies were not statistically different from the latencies of the awake patients. Also in table 2, latencies of Na and Pa of the patients with and without implicit memory are compared within every experimental group. There is a marked statistically significant increase of Na and Pa latencies in the patients without implicit memory in the isoflurane–fentanyl and the propofol–fentanyl groups, whereas in the two patients with implicit memory in the isoflurane–fentanyl and the propofol–fentanyl groups, Na and Pa latencies increased only slightly. There was also only a small increase of Na and Pa latencies in the patients of the flunitrazepam–fentanyl group who showed implicit memory postoperatively. In contrast, Na and Pa latency increases were statistically significant in the patients

**Table 2. Latencies of the Peaks V, Na, and Pa (in ms) for the Patients with and without Implicit Memory**

| Group | Patients | n | | Awake | | | Before Audiotape | | | After Audiotape | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | V | Na | Pa | V | Na | Pa | V | Na | Pa |
| All patients | With implicit memory | 7 | x ± SD | 5.88 (0.32) | 18.7 (1.68) | 30.1 (2.97) | 6.48 (0.48) | 20.1 (4.45)† | 36.6 (5.52)† | 6.42 (0.32) | 20.9 (5.26)† | 36.7 (5.61)† |
| All patients | Without implicit memory | 23 | x ± SD | 6.17 (0.24) | 19.0 (1.24) | 31.4 (3.21) | 6.78 (0.42) | 51.8 (12.9)* | 77.0 (10.5)* | 7.04 (0.38) | 47.9 (13.2) | 74.3 (16.2) |
| Group 1 (flunitrazepam plus fentanyl) | With implicit memory | 5 | x ± SD | 5.76 (0.33) | 18.8 (1.86) | 30.6 (3.47) | 6.48 (0.30) | 19.8 (1.69)† | 35.9 (2.67)† | 6.40 (0.24) | 19.1 (2.99)† | 35.4 (3.76)† |
| | Without implicit memory | 5 | x ± SD | 6.00 (0.32) | 19.0 (1.69) | 30.6 (3.78) | 6.35 (0.41) | 22.4 (1.21)* | 40.7 (1.95)* | 6.35 (0.41) | 23.4 (1.16)* | 41.0 (5.31)* |
| Group 2 (isoflurane plus fentanyl) | With implicit memory | 1 | x ± SD | 5.80 | 20.4 | 32.8 | 6.40 | 22.8 | 33.6 | 6.00 | 27.2 | 37.6 |
| | Without implicit memory | 9 | x ± SD | 6.17 (0.43) | 19.5 (1.42) | 32.7 (5.10) | 7.03 (0.52) | 55.8 (21.4)* | 78.2 (23.9)* | 7.42 (1.03) | 51.8 (21.8)* | 75.0 (24.9)* |
| Group 3 (propofol plus fentanyl) | With implicit memory | 1 | x ± SD | 6.00 | 17.2 | 26.6 | 6.40 | 18.2 | 37.4 | 6.60 | 21.2 | 35.6 |
| | Without implicit memory | 9 | x ± SD | 6.30 (0.28) | 18.3 (1.49) | 29.6 (2.09) | 6.62 (0.45) | 56.6 (17.9)* | 89.2 (19.8)* | 6.84 (0.52) | 51.7 (15.0)* | 84.9 (20.4)* |

The latencies of the peaks Na and Pa are significantly prolonged in the patients without implicit memory. In the patients with implicit memory, there are only slight increases of Na and Pa latencies compared to the awake state.

* $P < 0.01$ compared with awake.

† $P < 0.05$ compared with "without implicit memory."

of the flunitrazepam–fentanyl group without implicit memory postoperatively.

As shown in figure 4, we assigned our patients according to Pa latency increase of greater or less than 12 ms. Nine patients, including all patients with implicit memory (7 of 9), had a Pa latency increase of less than 12 ms. Twenty-one of 23 patients without implicit memory had a Pa latency increase of greater than 12 ms. These data indicate that in our study, the threshold of Pa latency increase of greater or less than 12 ms may provide sensitivity of 100% and specificity of 77% in distinguishing patients with implicit memory from patients without implicit memory postoperatively, and in predicting implicit recall with a probability of 77%.

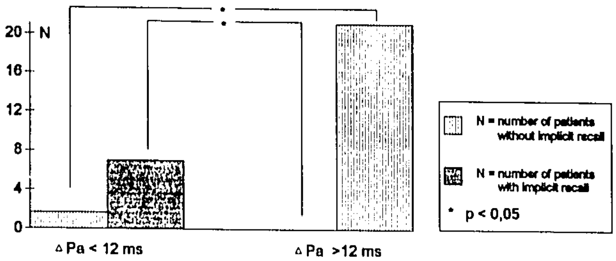


**Fig. 4. The patients assigned to two groups according to Pa latency increases of more than 12 and less than 12 ms. All patients with implicit memory were assigned to the group with a Pa increase of less than 12 ms. That means that a small increase of Pa correlates with a high incidence of implicit memory postoperatively. With a marked increase in Pa latency during anesthesia, no implicit memory could be observed.**

## Discussion

Our experiments showed the following main results. Auditory information could be recorded and retained during general anesthesia, but retrieval was mainly linked to an implicit memory system. Certainly, it may be possible that our patients consciously perceived the information at the time it was presented during surgery, but after surgery they had no conscious recollection of these experiences. Recall of intraoperatively presented auditory information was related to continued cortical processing of auditory stimuli, as evidenced by MLAEP behavior. Memory could be detected postoperatively when the early cortical potentials of the AEP remained nearly unchanged during general anesthesia compared to the awake state. In contrast, no recall could be observed postoperatively, when MLAEP were suppressed during anesthesia, indicating that auditory stimulus processing was blocked at the level of the primary auditory cortex.

Nevertheless, there also were some patients with preserved MLAEP during surgery who did not recall information from the audiotape postoperatively. This observation probably must be considered in the context of the limited test material used in the current study. Furthermore, it may indicate that MLAEP are a necessary, but not in every case sufficient, prerequisite for the processing, encoding, and retrieval of auditory information. We chose a threshold for the Pa latency increase during anesthesia of greater or less than 12 ms. In this way, 100% sensitivity but only 77% specificity were provided, indicating that a latency increase of less than 12 ms (*i.e.*, MLAEP relatively unaffected compared with the awake state) is a necessary but not sufficient condition to distinguish patients with implicit from those without implicit recall.

In contrast to these implicit memories, we could not demonstrate definitive explicit memories postoperatively, probably because the task we used to measure explicit memory (asking the patients to recall anything they may have perceived during anesthesia) was insensitive. Nevertheless, our results agree with the observations of others, who found only few explicit memories postoperatively. There was no free recall of an intraoperatively presented short story[24] or word list.[25] Only vague memories have been reported after the intraoperative presentation of personal messages or music in 5–7% of tested patients.[26] Patients recalled a sequence of digits presented at the end of the operation, when the effect of general anesthesia had decreased, but not digits presented during the surgical procedure.[27]

Nevertheless, several studies have shown a recall of intraoperatively presented auditory stimuli when information had to be retrieved implicitly, indicating that implicit tasks apparently are a more sensitive measure of memory during anesthesia than are explicit tasks. Millar and Watkinson[28] demonstrated that patients who had heard a list of words during general anesthesia scored significantly better on a postoperative recognition task than did patients of the control group, who had heard a tape of radio static during the operation. In studies by Jelicic *et al.*[29] and Roorda-Hrdlickova *et al.*,[30] patients postoperatively displayed implicit memory for target words that had been presented during anesthesia, compared to the control group, who had been presented with seaside sounds during the operation. Block *et al.*[31] found postoperatively implicit memory in a word completion task and memory for nonsense words presented during anesthesia. In a study by Bethune *et al.*,[32] patients undergoing coronary artery bypass grafting displayed postoperatively implicit recall for word associations presented during surgery and during emergence from general anesthesia.

Some investigators have demonstrated implicit learning during anesthesia when suggestions are given intraoperatively in an attempt to change postoperative behavior or feelings. Bonke *et al.*[33] reduced the duration of the postoperative hospital stay in a group of patients who heard positive suggestions during general anesthesia. Evans and Richardson[34] exposed patients either to recorded therapeutic suggestions or to a blank tape. The patients in the suggestion group spent significantly less time in the hospital after surgery, had a shorter period of postoperative pyrexia, and recovered better than expected when compared to the control group. McLintock *et al.* reduced the postoperative requirements of analgesic agents by presenting suggestions intraoperatively to patients who were to receive patient controlled analgesia postoperatively.[35] Bennett *et al.* observed that patients more often touched their earlobe when suggestions for these gestures were given intraoperatively.[36] Patients who were instructed during anesthesia to touch either their ear or their nose touched the suggested body part longer than the other part.[31] In a study by Goldmann *et al.*,[22] patients who intraoperatively had received the suggestion to touch their chin did so significantly more often during a postoperative interview than did patients who had not received these intraoperative behavioral suggestions.

Although these studies provided evidence of implicit memory during general anesthesia, several studies were not able to replicate these positive results. Dwyer *et al.*[37] studied the effects of isoflurane and nitrous oxide at subanesthetic concentrations on memory in volunteers. Implicit memory was prevented by 0.45 MAC isoflurane. Block *et al.*[38] were unable to prove the efficacy of intraoperative therapeutic suggestions for improved postoperative recovery in patients undergoing a variety of surgical procedures. Westmoreland *et al.*[39] could not show implicit memory or significant effects of priming during general anesthesia using free association, category member generation, and homophone spelling tasks. Cork *et al.*[40] were unable to demonstrate significant priming effects in a free-association test presented during general anesthesia.

Taken together, the studies cited above have not presented uniform results, and therefore, the phenomenon of implicit memory during general anesthesia still requires study. Likewise, Ghoneim and Block[41] point out that the mechanisms of actions of the different drugs on memory still must be analyzed in detail and that the concentrations of the commonly used anesthetics that prevent explicit and implicit recall still need to be determined. In our study, implicit recall was related to continued presence of MLAEP. MLAEP monitoring during anesthesia therefore might be useful for investigating doses and concentrations of general anesthetics that reliably block conscious and unconscious perception and explicit and implicit memory during anesthesia.

Our data on MLAEP agree closely with data obtained by Thornton *et al.*[42] and Newton *et al.*[43] They studied the relation between MLAEP and conscious awareness, explicit conscious recall, and response to verbal commands in surgical patients and anesthetized volunteers during anesthesia with different sub-MAC concentrations of nitrous oxide and isoflurane. When MLAEP peak latencies were significantly increased compared with the awake state, no conscious awareness, recall, or response to verbal commands could be observed. In contrast, when MLAEP were slightly increased during anesthesia, they found a high incidence of response to verbal commands and postoperative recall. The AEP variables were significantly related to the level of response and recall, fitting response and recall more closely than end-expiratory gas concentrations.

Our results indicate that it is possible to demonstrate memory for information presented during general anesthesia when a sensitive, implicit memory task is used to assess memory. Implicit memory is linked to the early cortical potentials of the auditory evoked response. The electrophysiologic data give evidence that stimulus transmission up to the level of the midbrain does not lead to explicit or implicit memory. In contrast, spared information processing in primary sensory cortices, as evidenced by MLAEP, can result in postoperative memory for intraoperative information. MLAEP reflect the level of auditory processing during general anesthesia and must be considered as a functional prerequisite for the cortical processing, encoding, and retrieval of auditory information heard during general anesthesia.

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