Reports of Investigation

Median nerve evoked responses and explicit memory during recovery from isoflurane/nitrous oxide anesthesia

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Purpose: To evaluate median nerve somatosensory evoked responses during recovery from anesthesia in relation to clinical findings.

Methods: Twenty-two gynecologic patients received isoflurane in nitrous oxide for anesthesia. Midlatency somatosensory evoked responses (N20, P25, N35, P45, N50) were recorded the day before surgery (AWAKE), during steady state anesthesia (STABLE), and every five minutes after discontinuation of anesthesia until the patients were able to name a shown object correctly (RECOVERY). Next day the patients were questioned with a structured interview about their explicit memory of the immediate recovery period and classified into groups: No-MEM (no memory) and MEM (memory). Multivariate analysis of variance compared electrophysiological parameters at the different time points and between the two memory groups.

Results: During STABLE isoflurane/N₂O anesthesia, all cortical amplitudes were reduced ($P \leq 0.003$) and all latencies were prolonged compared with AWAKE ($P < 0.001$). At RECOVERY the latencies N35, P45, N50 remained prolonged ($P \leq 0.001$), while the amplitudes N20P25 and P45N50 were reduced in comparison to AWAKE ($P \leq 0.02$). The latencies P45 (48 ± 8 vs 61 ± 9 msec) and N50 (67 ± 12 vs 81 ± 10 msec) were shorter in the patients of the group MEM ($P \leq 0.03$) at RECOVERY.

Conclusion: The reversibility of anesthetic induced changes in amplitudes and latencies of median nerve somatosensory evoked responses reflected clinical awakening during emergence from isoflurane/nitrous oxide anesthesia. In the patients who had recall for the immediate recovery period, the reversibility of anesthetic induced changes of components P45 and N50 was faster than in patients without recall.

Objectif : Évaluer les potentiels évoqués somesthésiques du nerf médian en relation avec les constatations cliniques pendant la récupération de l'anesthésie.

Méthode : Vingt-deux patientes de gynécologie ont reçu une anesthésie avec un mélange d'isoflurane et de protoxyde d'azote. Les potentiels évoqués somesthésiques de milatence (N20, P25, N35, P45, N50) ont été enregistrés le jour précédant l'opération (VIGILE), pendant une période stable de l'anesthésie (STABLE) et toutes les cinq minutes après l'arrêt de l'anesthésie jusqu'à ce que les patientes puissent nommer correctement un objet désigné (RÉCUPÉRATION). Le jour suivant, on a interrogé les patientes lors d'une rencontre structurée au sujet de leur mémoire explicite de la période de récupération immédiate. On les a ensuite réparties en groupes : No-MEM (sans mémoire) et MEM (mémoire). L'analyse de variance multivariée a permis de comparer les paramètres électrophysiologiques entre les deux groupes à différents moments.

Résultats : Pendant l'action STABLE de l'anesthésie à l'isoflurane/N₂O, toutes les amplitudes corticales ont été réduites ($P \leq 0,003$) et tous les temps de latence ont été prolongés, comparés aux données VIGILES ($P < 0,001$). Pendant la RÉCUPÉRATION, les temps de latence N35, P45, N50 sont demeurés longs ($P \leq 0,001$), tandis que les amplitudes N20P25 et P45N50 ont été réduites, comparées aux amplitudes VIGILES ($P \leq 0,02$). Les temps de latence P45 (48 ± 8 vs 61 ± 9 msec) et N50 (67 ± 12 vs 81 ± 10 msec) ont été plus courts chez les patientes du groupe MEM ($P \leq 0,03$) à la RÉCUPÉRATION.

Conclusion : La réversibilité des changements, induits par l'anesthésique, d'amplitude et de temps de latence des potentiels évoqués somesthésiques du nerf médian correspondait au réveil clinique pendant la récupération de l'anesthésie à l'isoflurane/N₂O. Chez les patientes qui ont eu une mémoire immédiate de la récupération, la réversibilité des changements provoqués par l'anesthésique des composantes P45 et N50 a été plus rapide que chez les patientes sans souvenir.

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ASSESSING depth of anesthesia is a major concern of anesthesiologists in avoiding intraoperative awareness. The introduction of balanced anesthetic techniques involving neuromuscular blocking agents makes the assessment more difficult because respiratory patterns and spontaneous movements as signs of inadequate anesthesia are no longer available. Alternative approaches that have been proposed include a more direct measurement of central nervous activity using the spontaneous or evoked electroencephalogram.

Somatosensory evoked responses are used clinically to monitor neural structures at risk during neurosurgical, orthopedic, or vascular surgery. They can be obtained by repetitive presentation of a suitable stimulus to the pathway at risk.¹ There are three negative and two positive midlatency MnSSER wave components in the awake state.² The first component N20 probably represents the synaptic events triggered by the primary input volley at the contra-lateral cortical projection area of the hand, and generators are assumed to originate in the area 3 b of the primary sensory cortex (Brodmann's classification).³ Generators for the later deflections are less well-defined and may originate from both cortico-cortical connections and separate thalamo-cortical projections.^{4,5} Using brain electrical source analyses Srisa-an *et al.* demonstrated that N60 is most likely generated in area 1.⁶ However, despite several neurophysiological investigations using either electrocorticography or, more recently, results from magnetic responses to electrical median nerve stimulation in combination with imaging techniques, the different generators of the SEP components are still debated.⁷⁻⁹

As a possible application for monitoring depth of anesthesia, median nerve somatosensory evoked responses (MnSSER) have frequently been studied during induction and maintenance of anesthesia.^{10,11} Thornton *et al.* suggested that the effect of nitrous oxide on the subcortical waves reflected analgesia, while the later cortical waves were sensitive to the hypnotic potency of isoflurane.¹² In contrast, during emergence from anesthesia, MnSSER have rarely been recorded. Moreover, no study investigated MnSSER components in relation to memory function during anesthesia. However, midlatency auditory evoked potentials provide information on the possibility of perceptual processing during general anesthesia.¹³

This prospective study investigated the relationship between MnSSER and clinical signs of awakening during recovery from isoflurane/nitrous oxide anesthesia. We hypothesized that the anesthetic induced changes of midlatency MnSSER components would gradually

be reversed in relation to clinical awakening. Moreover, we hypothesized that, if the patients differ in explicit memory performance the reversibility of MnSSER changes would be delayed in the patients without recall for the recovery period.

Methods

Subjects

After approval by the ethical committee and written informed consent, 22 female patients (age: 39 ± 10 yr, weight: 65 ± 14 kg, height: 167 ± 10 cm, ASA classification I – II) scheduled for breast or lower abdominal gynecological surgery were included in the study. Patients with neurological diseases or who took CNS-active drugs were excluded.

Anesthesia

The patients received pre-medication with 7.5 mg midazolam *po* 45 min before induction of anesthesia with $0.3 \text{ mg} \cdot \text{kg}^{-1}$ etomidate and $1.5 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$ fentanyl followed by $0.1 \text{ mg} \cdot \text{kg}^{-1}$ vecuronium. After tracheal intubation, anesthesia was maintained with end-tidal isoflurane 0.6 Vol% in nitrous oxide (66%) in oxygen (Cicero EM, F. Dräger, Lübeck, Germany). If necessary, additional bolus injections of $0.5 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$ fentanyl were administered after 30–45 min according to the surgical procedure, if the mean arterial blood pressure and/or heart rate increased more than 20% compared to baseline values. After surgery, when the MnSSER-recordings had been performed, isoflurane and nitrous oxide were discontinued, and the lungs were ventilated with oxygen 100%. Controlled ventilation was continued as long as the patients tolerated the tracheal tube. When the patients started coughing or showed spontaneous movements and responded to a verbal command to take a deep breath, extubation was performed. Subsequently, oxygen was supplied via a facial mask. The MnSSER recording was continued until the patients opened their eyes spontaneously.

MnSSER acquisition

On the day before surgery, patients became accustomed to the experimental setting and comfortably relaxed with closed eyes in a supine position for MnSSER-recording (Evomatic 4000® system [Dantec, Copenhagen, Denmark]). The baseline MnSSER recordings were performed after the assessment of the individual stimulation thresholds. For unilateral stimulation of the median nerve (stimulation rate 3 Hz), a mounted dual stimulator (13L36, Dantec, Copenhagen, Denmark) with the cathode 2.3 cm from the anode produced monophasic rectangular pulses of 0.2 msec duration at the wrist. By preference the right median nerve was stimulated.

However, in five patients for whom dissection of axillary lymph nodes on the right side was planned for breast cancer, the left median nerve was stimulated. In relation to the individual sensory and motor thresholds first the threefold sensory threshold intensity and then the motor plus sensory threshold intensity was used as dummy blocks. Then the stimulation intensity was further increased to the individual threshold of tolerance and two baseline recordings were performed. The stimulation intensity was kept constant throughout the experiment. The MnSSER waveforms were recorded simultaneously on three amplifier channels using sterile platinum needle electrodes (13L70, Dantec, Copenhagen, Denmark) placed over the ipsilateral brachial plexus (Erb's point), the spinous process of the 6th cervical vertebra (C6) and the contralateral cortical hand area at the scalp (C3' or C4').² A mid-forehead reference electrode was used (Fpz; international 10-20 System) and electrode impedances were kept below 10 k Ω . The bandpass was set at 20 Hz to 2 kHz.^{1,4a} The device includes an automatic artefact rejection mode. For data acquisition, the digital resolution was 12 bits, the sampling rate was 25 kHz per channel, and the resolution 1000 points per channel. A post-stimulus period of 90 msec (180 msec during recovery from anesthesia) was analysed. For each response, 200 stimuli were averaged and stored on disk for later analysis. Latencies and amplitudes of MnSSER were obtained using a software package (EvoPC®, Müller, Hamburg, Germany). The following peak latencies were evaluated: at Erb N10; at C6 N13 and P17; at the scalp a w-shaped complex with the three prominent negative (N20, N35, N50) and two prominent positive components in between (P25, P45) occurring within 15 to 70 msec post stimulus after median nerve stimulation.² During anesthesia and recovery, the first prominent negative peak (occurring between 17-25 msec) was defined as N20 and the following components were subsequently examined.² The next positive wave was referred to as P25, the second negative peak was referred to N35, etc. Furthermore, the peak-to-peak amplitudes N13P17, N20P25, P25N35, N35P45, P45N50 and the central conduction time (CCT; latency N20 – latency N13) were calculated.

The MnSSER recording was performed the day before surgery (AWAKE), during steady state isoflurane/nitrous oxide anesthesia after the end of surgery (STABLE), and every five to ten minutes during recovery from anesthesia. In accordance with the clinical findings, Pre-EXT was defined as the last MnSSER-

recording before extubation and Post-EXT was defined as the first recording following extubation, when the patients opened their eyes on command. When the patients opened their eyes spontaneously, they were asked to define verbally a shown object (a small red booklet [about 12 $\times$ 15 cm in size], which was opened and closed in front of the patient). When they correctly named the shown object, they were asked to keep it in mind. Then, the final MnSSER recording was performed (RECOVERY).

Vital parameters and clinical findings

The electrocardiogram (HR; beats per minute), mean arterial blood pressure (MAP; mmHg), pulse oximetric oxygen saturation (SpO₂%), capnography for CO₂ (P_{ET}CO₂, mmHg), end expiratory isoflurane concentration (Iso_{ET} Vol %) and nitrous oxide (Vol %) concentrations during and after anesthesia (after extubation a tight face mask was used and the patients were instructed breathe in deeply), skin temperature of the stimulated arm and rectal temperature (C) were recorded simultaneously (Cicero EM, F. Dräger, Lübeck, Germany). The total time of anesthesia, the time of the extubation and the time when the patients were able to name the shown object were registered.

Memory

The day after the operation, the patients were asked, using a structured interview, about the immediate recovery period (Table I). Based on their answers they were classified into two groups: No-MEM - without memory; MEM - with explicit memory for the immediate recovery period.

Statistical analysis

Means and standard deviations of values for the various peak latencies, conduction times, and amplitudes were calculated. The distribution of data was tested with a Kolmogorov-Smirnov test. Numerical data regarding MnSSER components and vital parameters were subjected to repeated measures analysis of variance using Hotellings T-square.¹⁵ This statistical

TABLE I

Structured interview 24 hr after anesthesia:

- 1 What was the first you remembered after waking up from anesthesia?
- 2 Do you remember anything shown to you during the wake-up period?
- 3 Do you remember whether the MnSSER recording was performed?
- 4 Were you asked to keep anything in mind during recovery from anesthesia?

^a For further studies a high pass setting of 1-5 Hz is suggested (s. discussion)

TABLE II Vital parameters

	AWAKE	STABLE	Pre-EXT (9 ± 5 min)	Post-EXT (15 ± 5 min)	RECOVERY (22 ± 5 min)
	No-MEM / MEM	No-MEM / MEM	No-MEM / MEM	No-MEM / MEM	No-MEM / MEM
HR /min	71 ± 2 / 70 ± 2	67 ± 3 / 70 ± 4	73 ± 5 / 75 ± 6	89 ± 4 / 89 ± 6	89 ± 4 / 94 ± 6
MAP (mmHg)	90 ± 3 / 84 ± 4	80 ± 5 / 78 ± 4	98 ± 5 / 96 ± 6	102 ± 5 / 96 ± 5	92 ± 4 / 91 ± 4
SpO ₂ (%)	98 ± 1 / 99 ± 1	99 ± 1 / 99 ± 1	99 ± 1 / 99 ± 1	99 ± 1 / 99 ± 1	99 ± 1 / 99 ± 1
PCO ₂ (mmHg)		34 ± 1 / 35 ± 1	37 ± 2 / 38 ± 1	39 ± 1 / 37 ± 1	39 ± 1 / 38 ± 2
I _s q _T (%)		0.6 ± 0.1 / 0.6 ± 0.1	0.2 ± 0.1 / 0.2 ± 0.1	0.1 ± 0.1 / 0.1 ± 0.1	0.1 ± 0.1 / 0.1 ± 0.1
N ₂ O _{ET} (%)		61 ± 4 / 60 ± 5	17 ± 6 / 13 ± 4	7 ± 2 / 8 ± 2	4 ± 1 / 5 ± 2
Rectal TEMP (°C)	36.4 ± 0.3 / 36.7 ± 0.4	35.3 ± 0.3 / 35.7 ± 0.2	35.3 ± 0.4 / 35.7 ± 0.2	35.5 ± 0.4 / 35.9 ± 0.2	35.5 ± 0.4 / 35.9 ± 0.2

Means ± SD of heart rate (HR), mean arterial blood pressure (MAP), pulse oxymetric oxygen saturation (SpO₂), end expiratory carbon dioxide (PCO₂), isoflurane (Iso_{ET}) and N₂O (N₂O_{ET}) concentrations and rectal body temperature (TEMP) before, during steady state isoflurane/nitrous oxide anesthesia and during emergence from anesthesia. No-MEM = patients without memory of the wake-up phase, MEM = patients with memory. Measurements were performed before (AWAKE), during isoflurane/nitrous oxide anesthesia (STABLE) and during recovery from anesthesia (Pre-EXTubation; Post-EXTubation, RECOVERY).

TABLE III MnSSER latency changes in relation to memory function

		AWAKE	RECOVERY
P45	No-MEM	41.5 ± 7.3	60.6 ± 7.8*
	MEM	39.4 ± 4.6	47.8 ± 8.1
N50	No-MEM	55.4 ± 6.5	81.1 ± 9.8*
	MEM	52.0 ± 5.9	67.3 ± 12.1

Means and SD of MnSSER latencies P45 and N50 before (AWAKE) and 22 ± 5 min after the end of isoflurane/nitrous oxide anesthesia (RECOVERY). The group No-MEM includes patients without explicit memory for the immediate wakeup phase (n = 9, evaluated 24 hr later), MEM includes patients who presented recall for the recovery period (n = 10). * = $P < 0.05$ between the two groups.

approach is most appropriate for studies involving repeated measurements in the same individual at different times, but has the disadvantage of being applicable only to complete data sets for all time points. For descriptive purposes, differences between different time points were analysed with paired t tests for all measurements.

Between group comparisons (MEM *vs* No-MEM) regarding the patients' characteristics and clinical findings were conducted by Students' t tests. Statistical comparisons of all MnSSER components were performed with multivariate analyses (Hotellings T-square; independent variable: memory) at AWAKE and RECOVERY between the memory groups. The multivariate comparisons at STABLE were limited to components N20, P25 and N35 due to missing data, when the components of the later MnSSER components were suppressed during anesthesia. $P < 0.05$ was adopted for level of significance for all statistical tests.

Results

Vital parameters and clinical findings

The mean time of anesthesia was 96 ± 36 min. The patients received 0.2 ± 0.05 mg fentanyl in addition to the induction dose with a mean interval of 61 ± 18 min before the end of anesthesia. Tracheal extubation was performed 12 ± 5 min after the end of anesthesia. At 22 ± 5 min after discontinuation of anesthesia the patients were able to name the shown object correctly. During the wake-up phase, the hemodynamic parameters were stable. There was no request for any additional medication. At RECOVERY the patients reported no pain.

The day after the operation, 19 patients could be interviewed about their memory for the recovery period, because three had already been discharged from the hospital. While nine patients did not remember the wake-up phase, 10 showed explicit memory. Seven patients remembered the shown book, and three recalled the electrical stimulation of the median nerve at their wrist. Only two of the seven patients who remembered the shown object recalled the nerve stimulation as well. There were no differences in demographics, fentanyl consumption or delivery, the time of the extubation, the time to identify the shown object correctly after anesthesia, the vital parameters or the end-tidal gas concentrations between the two groups (Table II). However, the time of anesthesia was longer in the group No-MEM than in the group MEM (110 ± 26 min *vs* 82 ± 31 min; $P < 0.05$).

MnSSER components

The mean stimulation intensity was 12 ± 3 mA, while the motor threshold reached 6 ± 3 mA. All cortical MnSSER components were well defined preoperatively except P45, which was absent in one patient, and N50, which

FIGURE 1 Means $\pm$ SD of latencies of MnSSER components before (AWAKE), during steady state isoflurane/nitrous oxide anesthesia (STABLE) and during recovery from anesthesia (Pre-EXT = before extubation, Post-EXT = after extubation, RECOVERY = 22 $\pm$ 5 min after discontinuation of isoflurane/nitrous oxide). N = 22 patients, * = $P < 0.05$ vs AWAKE.

FIGURE 2 Means $\pm$ SD of amplitudes of MnSSER components before (AWAKE), during steady state isoflurane/nitrous oxide anesthesia (STABLE) and during recovery from anesthesia (Pre-EXT = before extubation, Post-EXT = after extubation, RECOVERY = 25 $\pm$ 5 min after discontinuation of isoflurane/nitrous oxide). N = 22 patients, * = $P < 0.05$ vs AWAKE.

was absent in two patients. Satisfactory traces were obtained in all patients during steady state anesthesia and the wakeup phase. The Kolmogorov-Smirnov test supported the assumption of normal distribution for all MnSSER parameters. The multivariate analyses revealed differences for CCT and all cortical latencies, comparing the awake values with the components during anesthesia and the measurements during the wakeup phase ($P < 0.004$). Figure 1 summarises the results for the latencies

FIGURE 3 MnSSER latency components P45 and N50 before (AWAKE) and 22 $\pm$ 5 min after discontinuation of isoflurane/nitrous oxide (RECOVERY). Group No-MEM (n = 9) includes patients without memory for the immediate recovery period, while group MEM (n = 10) includes patients with explicit memory function evaluated 24 hr later.

FIGURE 4 Midlatency MnSSER components (90 msec post-stimulus interval, C3' vs Fpz) due to electrical stimuli delivered to the right median nerve at the wrist before (AWAKE), during steady state isoflurane/nitrous oxide anesthesia (STABLE) and during recovery from anesthesia (Pre-EXT = before extubation, Post-EXT = after extubation, RECOVERY = 25 min after discontinuation of isoflurane/nitrous oxide) in a female subject with recall for the wakeup phase, 32 yr, ASA I.

of the different peaks. An interaction between latency components and time revealed a more pronounced effect on the later MnSSER waves ($P = 0.0002$). The importance of this effect is remarkable regarding the higher between-subject variance in those components which tends to mask effects in the inferential statistical analysis. Mean values of cortical peak-to-peak midlatency amplitudes are shown in Figure 2.

During STABLE the primary cortical complex N20P25 remained identifiable in all patients. In contrast, at STABLE, N35 was identified in only 18 patients, P45 in 13 and N50 in 11 patients. The latencies of the cortical components and CCT were significantly prolonged (5.6 ± 0.6 msec *vs* 7.4 ± 1.3 msec, $P < 0.001$). The amplitudes N20P25 and P25N35 decreased significantly ($P < 0.001$), while the later amplitudes were suppressed in almost half of the patients.

During emergence from anesthesia, the MnSSER changes were gradually reversed. In comparison to AWAKE, all latencies and CCT remained prolonged ($P \leq 0.03$) at Pre-EXT. In comparison to STABLE CCT (6.6 ± 1.1 msec) and all latencies except N50 ($P = 0.06$) were significantly reduced ($P \leq 0.04$) at Pre-EXT. N35 was still absent in one and P45 in three patients, while nine patients did not present N50. The amplitudes N20P25 and P25N35 remained reduced in comparison to AWAKE ($P < 0.001$), while they increased compared with STABLE ($P < 0.001$). After extubation, when the patients opened their eyes on command (Post-EXT), the latencies were still prolonged in comparison to AWAKE ($P \leq 0.05$). CCT (5.9 ± 1.1 msec) and the amplitude P25N35 regained baseline level. The prolongations of all latencies and CCT were further reduced in comparison to STABLE ($P < 0.01$). The N35 remained suppressed in one patient, P45 in two, and N50 in six patients. At RECOVERY the latencies of components ≥ 35 msec were still prolonged ($P \leq 0.001$) in comparison to AWAKE, while the amplitudes N20P25 ($P < 0.02$) and P45N50 ($P = 0.002$) remained reduced. P45 was absent in one and N50 in three patients.

MnSSER and memory

At RECOVERY the patients in the group No-MEM showed prolonged latencies for the components P45 and N50 in comparison to the patients of the group MEM ($P \leq 0.03$; Table III, Figure 3). The amplitudes and the latencies of N20, P25 and N35 did not differ between the two groups. During the awake state, statistical analysis did not reveal differences in the MnSSER components between the two groups. Moreover, N20, P25 and N35 did not differ during anesthesia. The components P45 and N50 were excluded from the group comparison during STABLE, because they were suppressed in almost half of the patients during anesthesia and the number of observations was too small for statistical analysis. Figure 4 gives an example of the typical MnSSER traces with the identification of the various components of one patient who remembered the MnSSER recording at RECOVERY. The anesthetic induced MnSSER changes were almost completely reversed at RECOVERY in this patient.

Discussion

In the present study we investigated anesthetic induced changes of midlatency MnSSER components during steady state and recovery from isoflurane/nitrous oxide anesthesia in relation to clinical findings and awake baseline values. We demonstrated during 1 MAC isoflurane/nitrous oxide anesthesia, that the anesthetic effects increased with the latency of the cortical MnSSER components, which is in agreement with previous studies including non-specific later MnSSER components.^{1,6} When, during recovery from anesthesia, the patients opened their eyes spontaneously and were able to name a shown object correctly, CCT and the latencies of N20 and P25 had regained baseline levels. In contrast, the components ≥ 35 msec remained prolonged in latencies and indicated impaired cortical processing of sensory stimuli.

In addition, we demonstrated that the MnSSER latencies P45 and N50 were reduced in the patients who recalled the immediate wakeup phase after 24 hr in comparison with the patients without recall. The total time of anesthesia was longer in those patients without recall. Presumably the level of anesthesia differed among the patients due to the persistent uptake of isoflurane in the different body compartments. Subsequently, patients had a higher residual of volatile anesthetics. This was not reflected in the endexpiratory gas concentrations, which did not differ in both groups. Moreover, the time of extubation and the time when the patients were able to name a shown object were similar. It remains open whether a more detailed clinical investigation including cognitive or motor tasks performances would have revealed other differences between the two groups.

It is generally accepted that isoflurane prolongs the latencies and reduces the amplitudes of cortical components in a dose-related manner.^{10,17} Nitrous oxide has been shown in volunteers to reduce the N20 amplitude without a change in latency and is known to have an additional effect on isoflurane in depressing cortical MnSSER components.^{18,19} In eight patients Thornton *et al.* identified a subsequent negative (N35) and positive deflection (P45) following N20-P25 complex during anesthesia.¹² They documented statistically different latency changes of N20 and P25 induced by isoflurane compared to nitrous oxide, while the latencies of two subsequent components were affected similarly by the two anesthetic agents. Isoflurane reduced amplitudes of P25-N35 and N35-P45 more profoundly, while the effect of nitrous oxide on the amplitude of the P15-N20 and the N20-P25 response was stronger. The difference was statistically significant for P15-N20 only. The authors suggested

that the effect of nitrous oxide on the subcortical waves reflected analgesia, while the later cortical waves were sensitive to the hypnotic potency of isoflurane. The comparison with our results remains limited due to differences in methods and statistical analysis. To support a differential effect of nitrous oxide and isoflurane a further study with graded changes of the concentration of one agent at a time is needed.

When interpreting our results, several factors must be taken into consideration which contribute to minor changes in evoked responses. Changes in heart rate and arterial pressure indicated different steps of recovery from anesthesia clinically, while capnometry reflected the anesthetic effect on respiratory function. Despite efforts to maintain body temperature, a decrease of 1°C occurred. However, it has been shown in previous studies that minor changes in body temperature, hypercarbia and blood pressure do not interfere substantially with evoked response monitoring.²⁰⁻²² To avoid further variation, the intensity of stimulation was kept constant in the present investigation. It has been shown that increasing stimulation intensity changes the evoked responses amplitudes.²³

In addition, the use of fentanyl and the surgical trauma might have influenced our results. Previous studies indicated an increase in the amplitudes N20P25 and P25N35 during surgical periosteal preparation under isoflurane/nitrous oxide anesthesia.¹¹ Unfortunately there is no systematic study of the effect of small doses of fentanyl on evoked responses comparing the stimulated (intubation, skin incision) and the unstimulated patient. During stable isoflurane anesthesia (0.4 MAC) with remifentanyl, Crabb *et al.* documented an increase in the amplitudes of P25N35 and N35P45, while N20P25 decreased with remifentanyl in the unstimulated patient.²⁴ It is known from studies with the bispectral index (derived from the spontaneous electroencephalogram by a complex signal analysing technique), that the adjunctive use of opioids confounds the interpretation of the index as a measure of anesthetic adequacy predicting movement to skin incision.²⁵

We showed, in this study, that the later MnSSER components (≥ 35 msec) are particularly sensitive to different levels of sedation and consecutive cognitive impairment. Similarly, it is known from the midlatency auditory evoked responses that Pa and Nb components, occurring approximately 30 and 40 msec post-stimulus, are promising markers for changes in consciousness during anesthesia.²⁶ However, the generators of the later MnSSER components are still debated and the nomenclature differs in relation to different recording techniques.²⁷ However, they have been shown to be early markers for cognitive impairment in patients with

hepatic encephalopathy for example.²⁸ While in the present study the highpass was chosen according to the IFCN standard for recording the primary cortical complex N20-P25, for the later components a high pass setting between 1 and 5 Hz is suggested for further studies.¹⁴ Moreover, a lower stimulation frequency about 1 Hz would be appropriate.

We were able to document that the anesthetic induced changes of the MnSSER components P45 and N50 were less pronounced in the patients who recalled the immediate recovery period 24 hr later. Further clarification is needed, whether the MnSSER changes are directly related to impaired memory function or it is a coincidental finding related to a common cause. Using a structured interview to assess recall of the recovery period is a rather global and perhaps less precise test of memory function. Cognitive functions are related to different cortical neuronal structures which are linked to each other by numerous synaptic processes at the cerebrum. Assessing cerebral function related to learning and memory in volunteers or patients is complex.^{29,30} Memory research investigating different states of consciousness due to anesthetics seems to be even more complicated.³¹ However, the midlatency components of auditory evoked responses have been shown to correlate with preservation of implicit memory function during anesthesia.³² Van Hooff *et al.* demonstrated that event-related potentials recorded intraoperatively during cardiac surgery correlated with postoperative memory.³³ Further studies are needed to clarify to what extent midlatency MnSSER components can be used as a tool to evaluate the likelihood of preserved memory function during anesthesia.

In conclusion, the present study demonstrated the practicability and feasibility of recording MnSSER during the early recovery period from isoflurane/nitrous oxide anesthesia. The midlatency MnSSER components offered information about the reversibility of the anesthetic state during the process of clinical awakening. Concomitantly, the MnSSER latencies differed among patients with and without recall. It seems worthwhile to examine MnSSER changes occurring during the various phases of recovery at subanesthetic concentrations of isoflurane in order to determine whether there is a correlation with evidence of awareness and whether MnSSER do supply additional information to the spontaneous electroencephalogram or auditory evoked responses.

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