Anesthesiology 2001; 95:1141–50

Wavelet Analysis of Middle Latency Auditory Evoked Responses

Calculation of an Index for Detection of Awareness during Propofol Administration

Eberhard Kochs, M.D., Gudrun Stockmanns, Ph.D.,† Christine Thornton, Ph.D.,‡ Werner Nahm, Ph.D.,§ Cor J. Kalkman, M.D., Ph.D.‖*

Background: **Middle latency auditory evoked responses (MLAER) as a measure of depth of sedation are critically dependent on data quality and the analysis technique used. Manual peak labeling is subject to observer bias. This study investigated whether a user-independent index based on wavelet transform can be derived to discriminate between awake and unresponsive states during propofol sedation.**

Methods: **After obtaining ethics committee approval and written informed consent, 13 volunteers and 40 patients were studied. In all subjects, propofol was titrated to loss of response to verbal command. The volunteers were allowed to recover, then propofol was titrated again to the same end point, and subjects were finally allowed to recover. From three MLAER waveforms at each stage, latencies and amplitudes of peaks Pa and Nb were measured manually. In addition, wavelet transform for analysis of MLAER was applied. Wavelet transform gives both frequency and time information by calculation of coefficients related to different frequency contents of the signal. Three coefficients of the so-called wavelet detail level 4 were transformed into a single index (Db3d4) using logistic regression analysis, which was also used for calculation of indices for Pa, Nb, and Pa/Nb latencies. Prediction probabilities for discrimination between awake and unresponsive states were calculated for all MLAER indices.**

Results: **During propofol infusion, subjects were unresponsive, and MLAER components were significantly depressed when compared with the awake states ($P < 0.001$). The wavelet index Db3d4 was positive for awake and negative for unresponsive subjects with a prediction probability of 0.92.**

Conclusion: **These data show that automated wavelet analysis may be used to differentiate between awake and unresponsive states. The threshold value for the wavelet index allows easy recognition of awake *versus* unresponsive subjects. In addition, it is independent of subjective peak identification and offers the advantage of easy implementation into monitoring devices.**

MIDDLE latency auditory evoked responses (MLAER) are depressed by most anesthetics in a dose-dependent fashion.[1] During anesthesia, persistent MLAER may indicate insufficient blockade of auditory information processing with the risk of intraoperative awareness.[2,3] Thus, recording of MLAER has been proposed for assessment of depth of anesthesia. However, assessment of MLAER amplitudes and latencies critically depends on visual inspection of the waveform and manual labeling of peaks Pa and Nb. Recent work indicates that detection of MLAER peaks by visual inspection is strongly influenced by subjective experience, resulting in a large interobserver variability.[4]

An automated classification procedure that eliminates observer bias can be used as an approach toward online MLAER monitoring. Several methods have been proposed for online extraction of MLAER measures that can be used for monitoring purposes. Based on the MLAER waveform, a quantitative measure of anesthetics-induced changes in MLAER has been developed.[5,6] A different approach using autoregressive modeling of MLAER for extracting an MLAER index has shown that the time lag between MLAER recording and calculation of an index can be minimized to approximately 2 s.[7] Fourier transform has been used for characterization of the frequency contents of MLAER by decomposing the signal into different sine waves of infinite length. However, Fourier transform eliminates the time information, and the frequency resolution of transient signals may be deteriorated by application of time windows. Recently, wavelet analysis has been suggested as a new tool for analyzing event-related potentials (ERP).[8] The wavelet transform is analogous to Fourier transform, but instead of sine waves the fundamental waveform for the decomposition is a signal of finite length called *mother wavelet*. This mother wavelet can be chosen from a variety of different predefined wavelets to meet the specific characteristics of transient signals such as MLAER.

Unlike Fourier transform, wavelet analysis allows a representation of MLAER in the time *and* frequency domain. Thus, specific characteristics (*i.e.*, time course, wave shape, fine structural details, frequency contents related to time) can be evaluated, resulting in a set of

* Professor, Director, and Chair, § Assistant Professor, Klinik für Anaesthesiologie der Technischen Universität München, Klinikum rechts der Isar. † Assistant Professor, Fachgebiet Technische Informatik, Fachbereich Maschinenbau, Gerhard-Mercator-Universität Duisburg. ‡ Associate Professor, Anaesthetic Research Unit, Northwick Park Hospital. ‖ Professor of Anesthesiology, Department of Anesthesiology, University Medical Center, Utrecht, The Netherlands.

Received from the Klinik für Anaesthesiologie der Technischen Universität München, Klinikum rechts der Isar, München, Germany; Gerhard-Mercator-Universität Duisburg, Duisburg, Germany; the Anaesthetic Research Unit, Northwick Park Hospital, Harrow, United Kingdom; and the Department of Anesthesiology, University Medical Center, Utrecht, The Netherlands. Submitted for publication August 8, 2000. Accepted for publication June 8, 2001. Supported in part by grant No. BMH1-CT93-1506 from the European Community, Brussels, Belgium, and grant No. 261/98 from the Bayerische Forschungsstiftung, Munich, Germany. Presented in part at the annual meetings of the American Society of Anesthesiologists, San Diego, California, October 18–22, 1997, and Orlando, Florida, October 17–21, 1998.

Address correspondence to Dr. Kochs: Klinik für Anaesthesiologie, Technische Universität München, Klinikum rechts der Isar, Ismaninger Str. 22, 81675 München, Germany. Address electronic mail to: E.F.Kochs@lrz.tum.de. Reprints will not be available from the authors. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

coefficients that determine the best approximation of the underlying signal by the specific wavelet chosen. Once the optimized wavelet for a given set of biosignals such as MLAER has been defined, it may be integrated into an automatic online monitoring system. It does not require in-depth experience of neurophysiologic signals and is not subject to observer bias. As such, it can be used in research for assessment of adequacy of anesthesia or as a guide for titration of anesthetics by the anesthesiologist. The purpose of this study was to investigate the feasibility of wavelet analysis for characterization of MLAER and discrimination between awake and unresponsive states during varying propofol infusions.

Methods

After obtaining approval of the Institutional Ethics committee of the Northwick Park Hospital (Harrow, United Kingdom), written informed consent was obtained from 13 male volunteers (mean age, 30 yr; SD, 3 yr) and 40 surgical patients (19 women, 21 men; mean age, 38 yr; SD, 10 yr).

Groups 1 and 2

Seven volunteers in group 1 and six in group 2 were studied. Propofol in volunteers of both groups were titrated with repeated bolus doses of propofol (30 mg) to loss of response to verbal command. Group 1 was used for selection of optimal wavelet coefficients (see Logistic Regression) for best differentiation between awake and unresponsive states. Volunteers in group 2 were studied several months later than those in group 1. Every 30 s, subjects were asked to press the hand of the investigator. At the loss of a definite response to the command, subjects were classified as unresponsive. Thereafter they were allowed to awaken, propofol was titrated again to the same end point, and then they were finally allowed to recover fully. In each subject, three MLAERs (380 sweeps) were recorded per state (three awake, two unresponsive periods), each corresponding to a 1-min period.

Groups 3 and 4

In patients scheduled for elective surgery and who were not premedicated, propofol was titrated to loss of response to verbal command using a target controlled infusion of propofol (Diprifusor, Master-TCI; Becton Dickinson, Brezins, France). Three minutes before propofol infusion was started, all patients received either an intravenous injection of 0.1 mg/kg midazolam (group 3; n = 20) or an equivalent volume of saline (group 4; n = 20). Propofol target was set to 8 μg/ml. Three MLAER waveforms (380 sweeps) were obtained at two time points: (1) before starting the midazolam–saline injection; and (2) after loss of response to verbal command. All recordings were performed before the start of surgery.

Pooled Data

To derive an indicator that was independent of the study protocols used in this investigation, all data from group 1 to group 4 were combined for analysis (n = 53).

Middle Latency Auditory Evoked Response

Single-channel electroencephalograph was recorded from electrodes placed at the vertex and one mastoid using a specially designed amplifier described previously.[5] The ground electrode was placed at the contralateral mastoid. Electrode impedance was checked automatically and maintained below 5 kΩ. Binaural auditory stimulation (6.38 Hz) was performed with rarefaction clicks (70 dB above hearing level) using insert earphones (Oticon AW180, Oticon, Strandvejen, Denmark). No automatic artifact rejection was used. The raw electroencephalograph was sampled at a rate of 1 kHz and stored on a personal computer for offline analysis. The exact position of each click was marked in the raw data file, allowing offline MLAER averaging. To allow estimation of signal quality during the study period, the raw electroencephalograph and a moving MLAER average were continuously displayed on the monitor screen. An investigator blinded to treatment labeled the extremes of the MLAER peaks Pa and Nb manually after visual inspection of the MLAER and measured the corresponding amplitudes and latencies. In addition, averaged MLAER signals were processed using discrete wavelet decomposition up to detail level 6 with the Daubechies wavelet of order 3 (MATLAB® Wavelet-Toolbox; The MathWorks Inc., Natick, MA).

Middle Latency Auditory Evoked Response Parameters

To reduce the variability caused by artifact contamination or observer bias, MLAER parameters within states (awake, unresponsive) were averaged to obtain one value for each parameter and state, respectively. In groups 1 and 2, there were three different awake periods and two unresponsive periods. Because there were no differences either within the three periods of the awake state or within the two periods of the unresponsive state, all data of each state were pooled. Similarly, for each subject in groups 3 and 4, two sets of separately pooled MLAER parameters (awake, unresponsive) were used for statistical analysis. Standard anesthesia monitoring was conducted in all subjects (electrocardiogram, blood pressure, arterial oxygen saturation, end-tidal carbon dioxide tension, body temperature).

Wavelet Transform

A short review on wavelet-based signal analysis is presented in Appendix 1. The approach used here employs

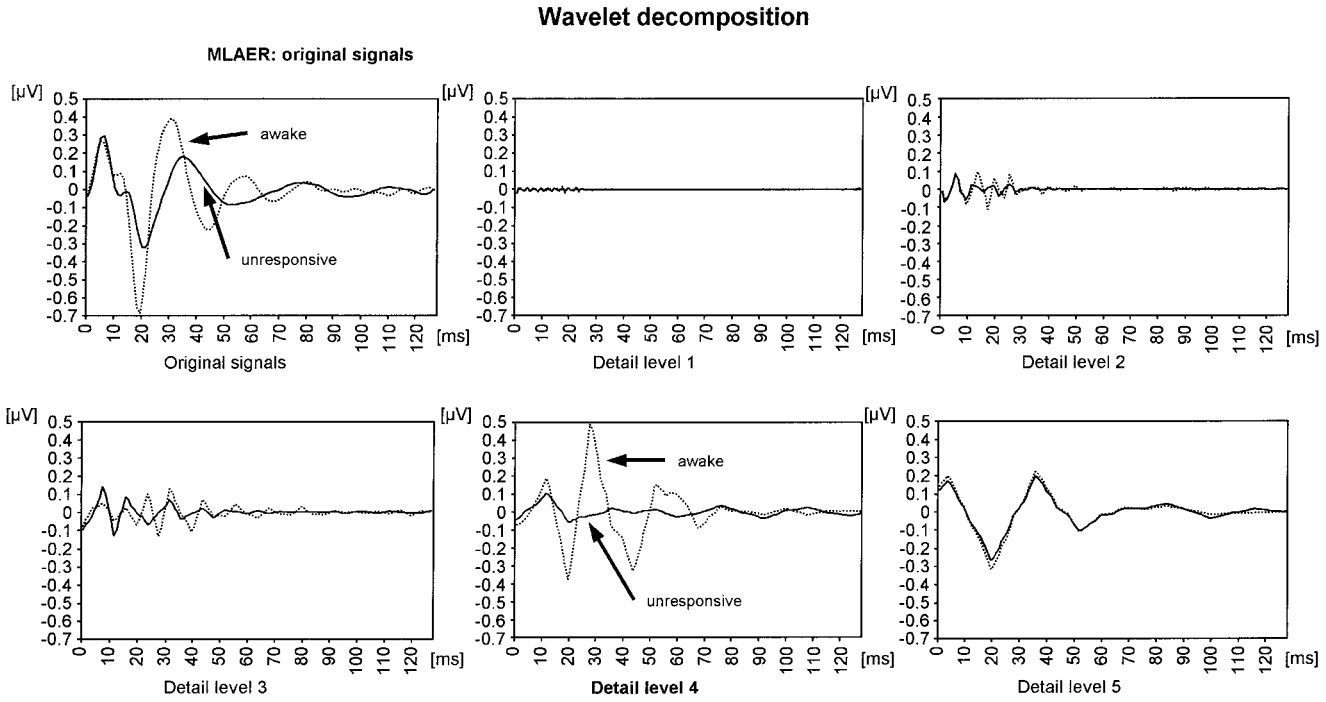

Fig. 1. Wavelet decomposition: original middle latency auditory evoked response (MLAER) signal (*top left*) and reconstructed signals using wavelet coefficients of the particular detail level. Grand average of signals of awake (dotted line) and unresponsive subjects (solid line) (number of epochs = 380).

a previously described application of wavelet analysis for ERPs.[8–11]

The familiar Fourier transform decomposes a waveform into a sine wave and a family of harmonics. The wavelet transform is analogous to the Fourier transform, but in place of simple sine waves of infinite duration, the fundamental unit of decomposition is a specific transient signal from a set of different functions called wavelets or, more specifically, mother wavelets. For analysis of a given class of signals, a specific mother wavelet has to be chosen for the best approximation of the signal characteristics (*i.e.*, peaks and troughs, frequencies). The frequency components of the signal can be calculated by transforming the signal into the time-frequency domain using different (dilated and shifted) versions of the same wavelet as "filters" (similar to Fourier transform). Unlike Fourier transform, which may not be applied to transient signals (*i.e.*, MLAER) and may lose information on the specific frequency contents of each component, the wavelet transform is an adequate tool for extraction of this type of information. For analysis of different frequencies of each signal, the wavelet has to be modified for each analysis step. In brief, a given signal is analyzed using a set of test functions that are derived by modifying the mother wavelet. These modifications include dilation of the mother wavelet (broadening or narrowing of the wavelet along the time axis) to extract the information about the underlying frequencies and shifting the mother wavelet along the x-axis to extract information about time with respect to the different peaks and troughs of each MLAER. The wavelet transform results in several coefficients representing different signal components related to the different applied versions of the mother wavelet. The special wavelet decomposition algorithm used for this analysis allows an extraction (in consecutive steps or levels, beginning with level 1) of the so-called "details" from the original signal (see Appendix 1: multiresolution analysis). These details represent different frequency components of the signal. Coefficients of one detail level are related to one dilated version of the mother wavelet and the corresponding shifted versions. The number of coefficients depends on the detail level. The lower the detail level, the higher the number of coefficients and the time resolution, and *vice versa*. Retransformation of the coefficients for different detail levels results in waveforms that reflect the temporal characteristics of the different frequency components (fig. 1).

Logistic Regression Analysis

For group 1 data, all coefficients of detail levels 1–5 were univariately tested for differences between the awake and unresponsive subjects (Mann–Whitney U test). As a result, three successive wavelet coefficients of detail level 4 were found to be highly significant ($P < 0.001$) for discrimination between these two states. These coefficients (d4_3, d4_4, d4_5) are located in the midlatency range of 20–60 ms and represent the oscillating waveform component in the detail level 4 plot of the reconstructed signals in figure 1.

For all groups, logistic regression was used to combine the three wavelet coefficients into a single index (Db3d4 = Daubechies wavelet 3, detail level 4) using a linear combination of a set of parameters given in equation 1. By this procedure, an index optimized for the reclassification of the awake and unresponsive groups was defined. Amplitudes were not used in this calculation.

$$\text{Db3d4: } = y_{Db3d4} = const_{Db3d4} + k_{1_{Db3d4}}d4\_3 + k_{2_{Db3d4}}d4\_4 + k_{3_{Db3d4}}d4\_5 \quad (1)$$

For the other MLAER parameters (Pa, Nb, Pa/Nb latency), indices were calculated in an analogous form:

$$\text{Pa: } = y_{Pa} = const_{Pa} + k_{1_{Pa}}\text{Pa latency}$$

$$\text{Nb: } = y_{Nb} = const_{Nb} + k_{1_{Nb}}\text{Nb latency}$$

$$\text{Pa/Nb: } = y_{Pa/Nb} = const_{Pa/Nb} + k_{1_{Pa/Nb}}\text{Pa latency} + k_{2_{Pa/Nb}}\text{Nb latency}$$

The linear coefficients k_{1_i}, k_{2_i}, k_{3_i} $i \in$ {Db3d4, Pa, Nb, Pa/Nb} represent the contribution (weight and sign) of the respective wavelet coefficients, and the constant values were calculated by finding a best fit of the logit function given in equation 2

$$p = \frac{1}{1 + e^{-y_i}} \quad (2)$$

using a maximum likelihood method, where p is the probability of observing the state "awake" for a given value of y_i, $i \in$ {Db3d4, Pa, Nb, Pa/Nb}.

Prediction Probability

A nonparametric measure for prediction probability, P_k, introduced by Smith *et al.*,[12] was calculated. Simplified, the P_k counts the probability p_c for two randomly chosen data points to indicate the level of anesthesia. If the indicator value of data point 1 is lower than the indicator value of data point 2, the observed levels of anesthesia for both cases are rank ordered in the same direction. This is called the concordance (p_c) case. Opposed to this case, there is the possibility that the two data points are rank ordered in the opposite direction (discordance [p_d]) or that data points from different observed anesthetic levels have the same indicator value (p_{tx})

$$P_k = \frac{p_c + 1/2p_{tx}}{p_c + p_d + p_{tx}} \quad (3)$$

From the definition of P_k in equation 3, it becomes clear that if the probabilities of discordance (p_d) and indicator indifference (p_{tx}) are both zero, P_k equals 1. If the probability of discordance equals that of concordance or if there is a high probability for p_{tx}, P_k equals 0.5. A value of P_k less than 0.5 means that the indicator and anesthetic depth behave inversely.

Statistical Evaluation

To detect differences between groups, parametric and nonparametric tests were used (SPSS 8.0.0; SPSS Inc. Chicago, IL). For demographic and hemodynamic data, the Student *t* test was used. MLAER indices (Pa, Nb, Pa/Nb) and Db3d4 index were compared using nonparametric Wilcoxon statistics. Paired sample tests were used for differences between awake and unresponsive states. Differences between different studies were tested for statistical significance using the Mann–Whitney U test. The null hypothesis was rejected at $P < 0.05$.

Results

Demographic Data and Hemodynamics

No differences were found with respect to demographic, hemodynamic, and ventilatory data between groups.

Pa and Nb Amplitudes and Latencies

Latencies and amplitudes for MLAER components Pa and Nb determined by visual inspection are given in table 1. All values were significantly different between awake and unresponsive states ($P < 0.001$). Administration of midazolam did not modify the differences in MLAER measures.

Linear coefficients for optimal classification of awake and unresponsive subjects were calculated using logistic regression for the individual Pa and Nb latencies and the combination of Pa and Nb latencies. Only small differences could be identified between the results of the logistic regression of the different groups for all MLAER indices (table 2). Therefore, coefficients of the pooled data set were used for comparison of the four different indices. Based on the linear coefficients of this pooled group, the index Db3d4 was calculated according to equation 1. Unresponsive subjects could clearly be discriminated from awake subjects. In addition, the wavelet index was the only measure that was able to discriminate between bolus injection of propofol and target controlled infusion. Because of the algorithm used for logistic regression, the threshold for differentiation between awake and unresponsive states could be set to zero. Thus, Db3d4 was negative for unresponsive states, whereas in awake subjects the index was positive (fig. 2). Coefficients of pooled data from all groups were used for comparison of the four different indices (Pa, Nb, Pa/Nb, Db3d4).

P_k Values

The probability of each index predicting the correct state is given in table 3. The lowest performance for

Table 1. MLAER Parameters in Awake and Unresponsive Subjects

		Awake		Unresponsive	
Drug	Parameter	Median	Percentiles (25–75%)	Median	Percentiles (25–75%)
Group 1 (n = 7)	Pa latency (ms)	30.8	29.2–33.8	39.9*	34.4–44.0
propofol (bolus)	Nb latency (ms)	42.8	41.2–44.5	55.2*	49.8–62.1
	Pa amplitude (μV)	0.78	0.59–1.08	0.39*	0.23–0.41
	Nb amplitude (μV)	0.76	0.57–1.05	0.33*	0.26–0.48
Group 2 (n = 6)	Pa latency (ms)	30.6	29.5–34.3	40.1*	34.6–44.5
propofol (bolus)	Nb latency (ms)	42.5	40.9–45.3	55.9*	50.2–63.4
	Pa amplitude (μV)	0.75	0.58–1.07	0.36*	0.26–0.42
	Nb amplitude (μV)	0.77	0.56–1.04	0.37*	0.22–0.53
Group 3 (n = 20)	Pa latency (ms)	31.7	29.7–34.0	40.8*	38.8–43.7
midazolam + propofol	Nb latency (ms)	43.3	41.5–47.2	59.3*	55.5–62.9
(TCI)	Pa amplitude (μV)	0.75	0.69–0.89	0.37*	0.21–0.51
	Nb amplitude (μV)	0.60	0.51–0.93	0.30*	0.18–0.52
Group 4 (n = 20) saline	Pa latency (ms)	31.1	29.4–32.7	39.8*	34.7–43.8
+ propofol (TCI)	Nb latency (ms)	43.3	41.3–44.3	56.5*	50.0–61.6
	Pa amplitude (μV)	0.82	0.61–1.06	0.34*	0.24–0.39
	Nb amplitude (μV)	0.78	0.56–1.01	0.35*	0.27–0.47

All parameters were significantly different between awake and unresponsive states.

* $P < 0.001$.

TCI = target controlled infusion.

discrimination between awake and unresponsive states showed the index Pa when compared with the other indices Nb, Pa/Nb, and Db3d4, respectively.

With respect to P_k for the correct clinical state, the user-independent indicator (index Db3d4) was at least as good in predicting the correct clinical state as the index Nb based on Nb latency (table 3).

Using the coefficients for the four MLAER indices derived from the pooled data, subjects belonging to groups 1–4 were reseparated and tested for differences between groups for both the awake and unresponsive state, respectively (table 4). Db3d4 was the only index that showed significant differences between the two volunteer groups and groups 3 and 4 (patients) in the unresponsive state. For the awake state, it is the only index showing no significant differences.

Discussion

The current study shows that wavelet transform of MLAER may be successfully used for classification of awake *versus* unresponsive states during propofol sedation. It was shown that the relevant information may be condensed into an index, called Db3d4. This index represents the respective time and frequency contents of the MLAER relevant to these clinical states. Similar to reports[13] on the manually determined latency of peak Nb, the index Db3d4 is able to discriminate between awake *versus* unresponsive states. An advantage of wavelet analysis for classification of MLAER changes is that it does not require visual inspection and manual peak labeling. It is thus free of observer bias and preserves the main characteristics of the signal in the time

Table 2. Linear Coefficients of Indices Calculated by Logistic Regression Analysis

		Group 1	Group 2	Group 3	Group 4
Coefficient (See Equation 1)	Pooled Data (All Groups)	Volunteers Propofol (Bolus)	Volunteers Propofol (Bolus)	Patients Midazolam + Propofol (TCI)	Patients Saline + Propofol (TCI)
$k_{1_{Db3d4}}$	1.3754	1.3261	1.8862	2.0915	1.3937
$k_{2_{Db3d4}}$	2.4295	1.4267	3.1189	6.4433	2.6352
$k_{3_{Db3d4}}$	−1.1766	−0.8645	−0.9281	−0.3956	−3.0203
$const_{Db3d4}$	−1.6187	−1.2997	−2.5971	−2.221	−1.7291
$k_{1_{Pa}}$	−0.3424	−0.3866	−0.4804	−0.2912	−0.3508
$const_{Pa}$	11.7728	13.0885	16.1136	10.0195	12.4481
$k_{1_{Nb}}$	−0.3424	−0.3527	−0.7619	−0.2917	−0.2818
$const_{Nb}$	16.4813	17.1153	35.9433	13.9285	14.0017
$k_{1_{Pa/Nb}}$	−0.0206	−0.0491	0.0092	0.1657	−0.1612
$k_{2_{Pa/Nb}}$	−0.3298	−0.3346	−0.7665	−0.4024	−0.1936
$const_{Pa/Nb}$	16.6547	17.8721	35.8586	13.5721	15.288

The linear coefficients contain an offset "constant," which describes the transform toward the threshold value between prediction values "0 = awake" and "1 = unresponsive." The other linear coefficients describe the relative amount of contribution of the parameters to the discrimination between 0 and 1.

TCI = target controlled infusion.

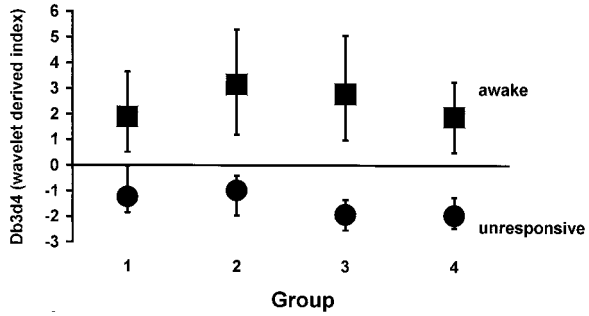

Fig. 2. Graphic representation of the results of the middle latency auditory evoked response wavelet-derived index Db3d4 (median and 25th, 75th percentiles). Evoked potentials from unresponsive subjects show an Db3d4 value less than zero. Waveforms from awake subjects result in an Db3d4 value greater than zero ($P < 0.05$). The index is calculated from equation 1 using linear coefficients from table 2 (pooled data).

domain. Because it is free of interobserver variability, it may be used as an objective measure of depth of hypnosis with the potential for implementation into future monitoring devices.

The midlatency components of auditory evoked responses have been extensively studied as a measure of depth of anesthesia.[2,14,15] MLAER-derived parameters have been shown to reliably indicate loss of consciousness.[6,16] In agreement with those studies, our data show that depression of MLAER during propofol infusion occurs when patients are unresponsive to verbal command.[1,14,16–18] After stopping the administration of propofol, subjects had regained responsiveness when Nb latency had decreased to less than 45 ms. These findings are in agreement with previous studies demonstrating that a decrease of Nb latency to less than 45 ms is related to an increased probability of intraoperative conscious awareness.[2,18]

It has become obvious that hemodynamic parameters are not sensitive enough to detect all instances of inadequate anesthesia. Therefore, many studies have tried to relate neurophysiologic measures to anesthetic drug effects. Most recently, an index calculated for the 40-Hz MLAER activity has been proposed for prediction of wakeful responsiveness.[19] Interestingly, in our study, the index Db3d4 reflecting wavelets of level 4 were able to discriminate between awake and unconscious states. The index most probably reflects 40-Hz activity.

In most clinical studies, the assessment of MLAER required visual inspection of the waveform by an experienced observer. In a previous study, we showed that agreement between experts on acceptable data quality of 180 evaluated MLAER was very poor, with an interobserver variability of 32%.[4] This suggests that results from different studies may not always be comparable. In addition, poor quality of intraoperatively recorded MLAER and interpretation by visual inspection may not be good enough for prospective guidance of titration of drugs. It is difficult to analyze MLAER in real time and to quantify changes in the clinical situation.[16] An alternative would be calculation of an automatically derived parameter that can be displayed online, similar to the median frequency,[20] spectral edge frequency[21] or Bispectral Index for electroencephalograph monitoring.[22] With the exception of some components of the composite Bispectral Index,,[23] until now spectral analysis of biosignals in anesthesia has been almost exclusively based on Fourier analysis. However, the required assumption that the signal is periodic is often not met. Fourier-based signal analysis of transient signals such as MLAER[24] may lose information about the frequency resolution of the signal with the risk of erroneous interpretations.

The technique of wavelet transform has been widely used in communication, geophysics, and ultrasonics. More recently, it was proposed for the analysis of biologic signals. The advantages of wavelet analysis for characterization of ERPs have been reviewed previously.[8] Wavelets may be used to represent the temporal characteristics of a signal by calculation of its spectral components in the time-frequency domain. For this purpose, different versions (dilated in time) of a specific test function of finite length (wavelet) are moved across the signal (shifting). By this procedure, the frequency contents of each part of the signal are calculated. The characteristic features of wavelets, which may be any zero mean function of finite energy, allow a translation of a signal in the time domain into a representation that is localized not only in frequency but also in time.[27] Unlike short-time Fourier transform, wavelet transform has the advantage of application of analysis windows of different lengths (representing the duration of different parts of signal) to the same signal. The corresponding window lengths are short at high frequencies and long at low frequencies. Thus, in contrast to short-time Fourier transform, which uses a fixed window in the time domain, wavelet analysis may be looked on as a scaling procedure to focus on different particular frequency contents of the signal by adequately modifying the length of the analysis window. The wavelet approach gives both good time resolution at high frequencies and good frequency resolution at low frequencies. Compared with Fourier transform, it results in improved evaluation of transient signals with varying frequency components that cannot fully be described in either time or frequency alone.

Table 3. P_k Values for Prediction of Awake Versus Unresponsive States

	Pa Index	Nb Index	Pa/Nb Index	Db3d4 Index
Mean P_k for reclassification	0.85	0.92	0.92	0.92

Pa, Nb, and Pa/Nb indices are based on the respective latencies. The index Db3d4 is calculated from special wavelet coefficients.

Table 4. Differences between Indices Derived from the Parameters Pa, Nb, and Pa/Nb Latencies and Special Wavelet Coefficients in Discriminating between Awake and Unresponsive States

	Awake			Unresponsive		
	Group 2	Group 3	Group 4	Group 2	Group 3	Group 4
Pa						
Group 1	*	—	—	—	†	†
Group 2	—	*	*	—	*	†
Group 3	—	—	—	—	—	—
Nb						
Group 1	†	—	—	—	*	†
Group 2	—	*	‡	—	—	—
Group 3	—	—	—	—	—	—
Pa/Nb						
Group 1	†	—	—	—	*	*
Group 2	—	*	‡	—	—	—
Group 3	—	—	—	—	—	—
Db3d4						
Group 1	—	—	—	—	‡	‡
Group 2	—	—	—	—	‡	‡
Group 3	—	—	—	—	—	—

* $P < 0.05$, † $P < 0.001$, ‡ $P < 0.0005$.

Bertrand *et al.*[25] demonstrated that, by means of an invertible wavelet transform, adaptive optimal filtering of auditory evoked responses that preserves the main characteristics of the signal can be achieved. Trejo and Shensa[26] compared wavelet transform with other feature or parameter extraction techniques, such as principal component analysis, to predict "human signal detection performance" by means of ERPs. When used in combination with linear regression and neural networks, representation of the ERP in the wavelet domain was adequate. In addition, the wavelet model required the smallest number of parameters when compared with principal component analysis and the raw data. According to Trejo and Shensa,[26] further advantages of the use of wavelet transform for parameter extraction are reduced computing time and increased efficiency. Furthermore, determination of ERP amplitudes and latencies by a human expert is more complex, subject to bias, requires more time, and cannot easily be applied online.

Our study demonstrates that wavelet-derived MLAER indices may be used for classification of awake *versus* unresponsive states during propofol administration. The P_k value calculated here suggests that results with respect to discrimination between awake and unresponsive states were as good as the more time-consuming visual-based analysis and manual identification of MLAER peaks. Moreover, it was the only index for differentiation between bolus administration and target controlled infusion of propofol. It can only be speculated if the performance of the wavelet index in this respect is related to an increased sensitivity for tracing the propofol effect site concentration. As the target concentration of propofol was not primarily titrated to unresponsiveness, a possible deeper level of sedation in the target controlled infusion group may be reflected by these differences. This interpretation may be supported by the slightly increased Nb latencies in the target controlled infusion groups.

This additional information can be attributed to the analysis of the frequency contents of the waveforms by wavelet analysis. In addition, our results indicate that MLAER analysis by wavelet transform is not biased by individual experience. Similar to a recently introduced auditory evoked response index[6] based on MLAER morphology, the wavelet-based index is easy to extract, reliable, not computationally intensive, and can be updated in short, clinically useful intervals.

One major advantage of our approach as compared with the method described by Mantzaridis and Kenny[6] seems to be that wavelet transform not only provides a feasible index with respect to discrimination between awake and unresponsive states, but also a representation of the underlying signal that preserves the temporal characteristics of different frequency components, allowing quality control of the MLAER acquisition process by the user (fig. 1). This kind of representation can be easily interpreted and integrated into monitor devices. This technique may therefore be a step forward toward a user-independent monitor of intraoperative auditory evoked responses. We believe that our approach holds promise for adequate representation of MLAER changes related to varying depths of anesthesia. However, we only investigated the end points (awake, unresponsive), and further studies must show if transitions from awake to unresponsive states and *vice versa* can also be traced adequately.

In conclusion, this study shows that wavelet transform can be used for characterization of MLAER. Our automated parameter extraction method is able to discriminate between awake and unresponsive states during propofol infusion. Wavelet-derived parameters were at least as good as the traditional procedure of peak label-

ing by visual inspection, and the analysis algorithm can be easily implemented for online analysis.

The authors thank D. Droese, Technician, and G. Schäpers, M.S.c., Staff Member, Department of Anesthesiology, Technische Universität, Munich, Germany; and T. Marcu, Ph.D., Assistant Professor, Department of Technical Computation, Gerhard-Mercator Universität, Duisburg, Germany.

Appendix: Wavelet Transform

Mathematical methods that decompose waveforms can be used to characterize complex biosignals such as arterial blood pressure or the electroencephalograph. A widely used method for electroencephalograph analysis is the Fourier transform. It decomposes a signal into a series or family of sine waves.[27] Each of these waves (called test functions) is defined by frequency, phase, and amplitude. The decomposition by Fourier transform leads to coefficients quantifying the fractional amount of each test function that describes a specific frequency component of the signal.

As an example, the decomposition of a signal composed of three different frequencies (10, 30, and 60 Hz, unitary amplitude and no phase) is shown in figure 3. The sine wave (test function) of 10 Hz extracts only the 10-Hz component from the signal. The other considered frequencies are treated similarly. The main disadvantage of the Fourier transform is the lack of time information. For instance, if the signal in figure 3A is reversed in time (fig. 3B), then an identical result of transformation is obtained that does not discriminate between the two signals.

From a mathematical point of view, auditory evoked responses[13] belong to a different class of signals when compared with electroencephalograph signals. First, the auditory evoked response is a deterministic signal of finite length (*i.e.*, MLAER: 100 ms). In contrast, the electroencephalograph is a stochastic signal of "infinite" length (several seconds to minutes). Second, the frequency contents of the auditory evoked response change abruptly with time. Sharp peaks with short interpeak latencies are followed by broader peaks with longer interpeak latencies. It is therefore necessary to use an analysis method that provides both frequency and time information, such as wavelet transform.

The Fourier transform and wavelet transform both analyze a signal by means of basis functions or test functions. The Fourier transform uses only the family of sine waves. These can be seen as compressed and expanded versions (called "dialted versions") in time of a particular sine wave with specific frequencies (*i.e.*, test functions 1 and 2; fig. 3). The family of test functions used by the wavelet transform to characterize specific signals[27] is constructed by a more complex procedure. First, a specific test function (mother wavelet) has to be chosen. It can be any zero mean function of finite energy. Second, the family of functions can be built by a continuous dilation of the mother wavelet. This procedure enables the extraction of the frequency contents of the signal in the following analysis. Simultaneously, the test function is shifted along the time axis to analyze the respective contribution of each fraction of the underlying signal (fig. 4).

Figure 4 shows the decomposition of the signals presented in figure 3 by means of the wavelet transform. In this example, a wavelet called "Mexican hat"[28] is used. Different frequency components of the signal are extracted by dilated versions of the mother wavelet. Unlike the Fourier transform, the time information is now preserved by shifting the wavelet in time. Time reversal of the signal in figure 4A leads to a corresponding change in the computed coefficients of the wavelet

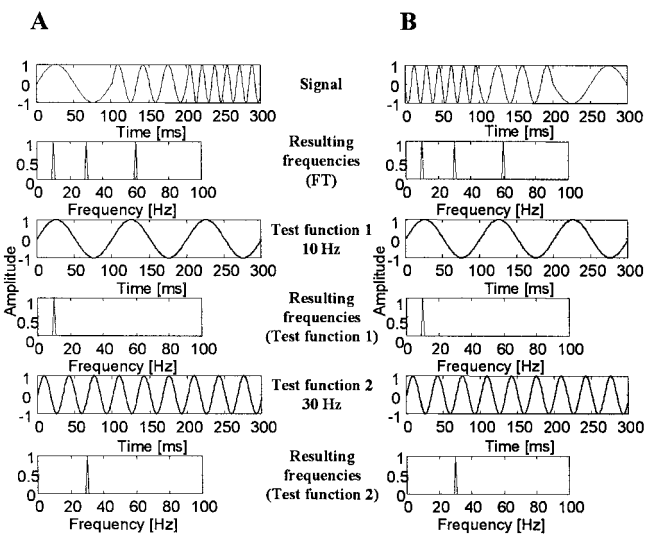

Fig. 3. Decomposition of a signal containing three distinct frequencies using the Fourier transform. (*A*) Original signal, (*B*) signal reversed in time.

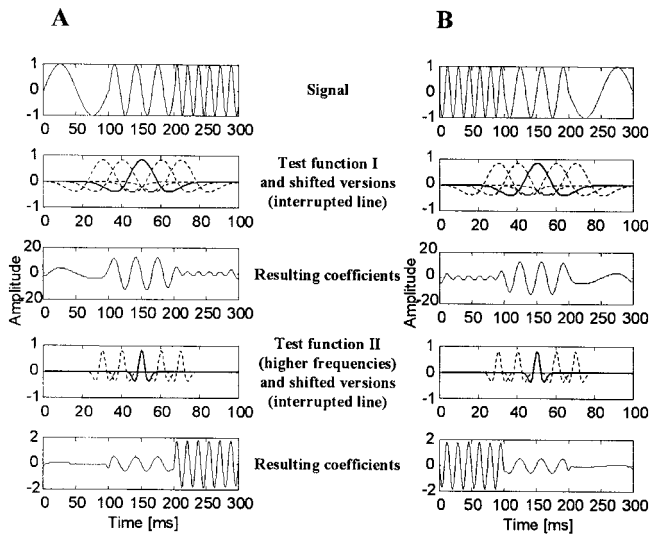

Fig. 4. Decomposition of the signal (fig. 3) using the wavelet transform. In contrast to Fourier transform, time information is preserved by wavelet transform.

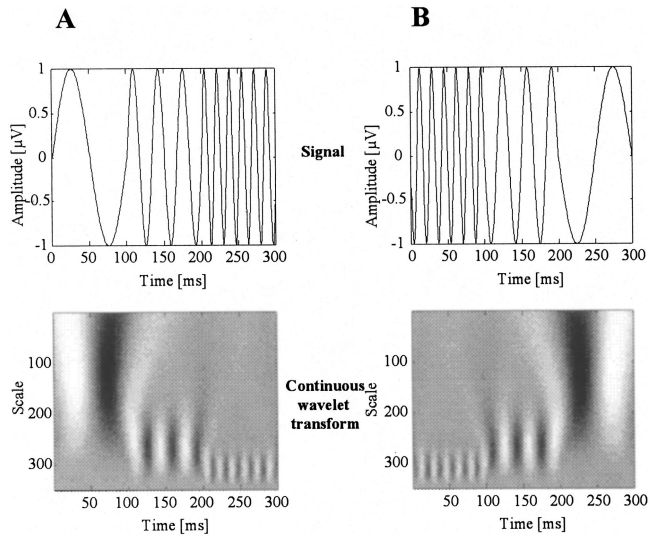

Fig. 5. Example of decomposition of the signal (fig. 3) using continuous wavelet transform. (*A*) Original signal, (*B*) signal reversed in time.

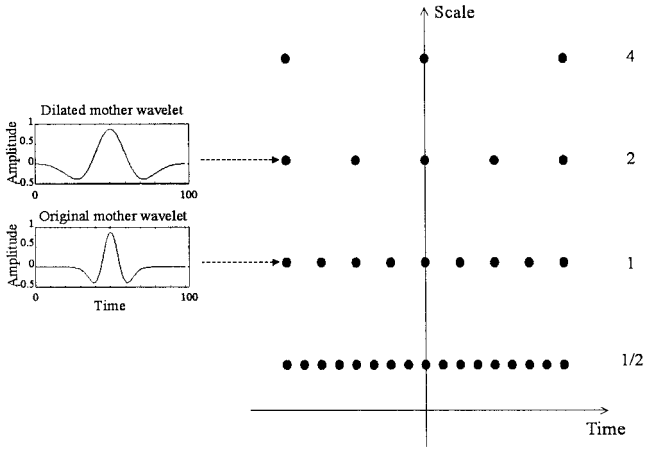

Fig. 6. Time and scale discretization used by the multiresolution analysis.

transform, which, in turn, now reflect changes over time (fig. 4B). This information is lost using the Fourier transform (fig. 3).

Figure 5 illustrates the complete time-frequency representation. Using the continuous wavelet transform, all dilated and shifted versions of the mother wavelet are represented. Frequency components are decomposed into different scales that are related to the diation factor of the underlying mother wavelet, *i.e.*, a high scale is associated with a low frequency and *vice versa*. The frequency information belonging to a certain time point is spread over several scales because of the resolution of the wavelet transform. In contrast, the frequency resolution given by the Fourier transform is sharp.

Similar to the Fourier transform, the biosignal may be analyzed continuously over time or in discrete steps (*e.g.*, every 1 ms). Because the modality of computation uses a family of linearly dependent test functions, the continuous wavelet transform contains redundant information. In contrast, the discrete version of the wavelet transform reduces the redundancy by using special discrete values for scales and positions in time.

The core for producing a fast algorithm for a discrete decomposition is represented by the multiresolution analysis.[28] This extracts the information based on independent (orthogonal) test functions[29] determined by a given number of scales and time positions (fig. 6). These numbers are dependent on the nature of the analyzed signal. The decomposition is performed using a bank of filters. Each pair of filters

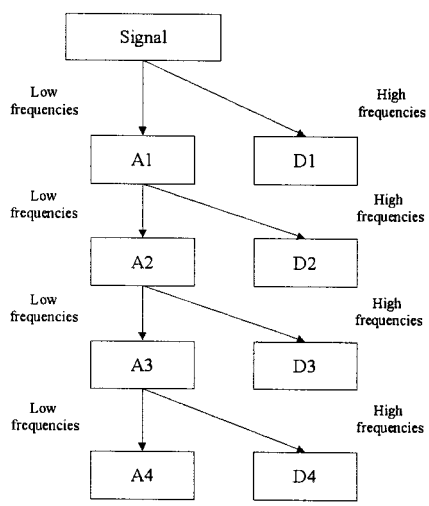

Fig. 7. Schematic representation of the multiresolution analysis approach.

from that bank corresponds to a (mother) wavelet function. At each level of analysis (representing the logarithm to the base 2 of the scale), the signal is high-pass and low-pass filtered (fig. 7). In addition, the number of points for which the time-frequency information is extracted is reduced by a factor of 2 to remove redundant information. At each stage, the low-pass–filtered signal is used for further processing.

At each stage of the multiresolution analysis (level), the high-pass–filtered signal is referred to as a *detail* and the low-pass–filtered signal as an *approximation* of that level. A specific number is used to indicate the corresponding level of analysis. For instance (fig. 7), A3 means approximation at level 3 and D3 stands for detail at the same level.

References

1. Thornton C: Evoked potentials in anaesthesia. Eur J Anaesthesiol 1991; 8:89–107

2. Thornton C, Barrowcliffe MP, Konieczko KM, Ventham P, Dore CJ, Newton DE, Jones JG: The auditory evoked response as an indicator of awareness. Br J Anaesth 1989; 63:113–5

3. Schwender D, Kunze-Kronawitter H, Dietrich P, Klasing S, Forst H, Madler C: Conscious awareness during general anaesthesia: Patients' perceptions, emotions, cognition and reactions. Br J Anaesth 1998; 80:133–9

4. Nahm W, Stockmanns G, Konecny E, Kalkman CJ, Thornton C, Bischoff P, Kochs E: Interobserver-variabilty for evaluation of middle latency auditory evoked potentials during anesthesia (abstract). ANESTHESIOLOGY 1998; 89:A942

5. Jordan C, Weller C, Thornton C, Newton DE: Monitoring evoked potentials during surgery to assess the level of anaesthesia. J Med Eng Technol 1995; 19:77–9

6. Mantzaridis H, Kenny GN: Auditory evoked potential index: A quantitative measure of changes in auditory evoked potentials during general anaesthesia. Anaesthesia 1997; 52:1030–6

7. Jensen EW, Lindholm P, Henneberg SW: Autoregressive modeling with exogenous input of middle-latency auditory-evoked potentials to measure rapid changes in depth of anesthesia. Methods Inf Med 1996; 35:256–60

8. Samar VJ, Swartz KP, Raghuveer MR: Multiresolution analysis of event-related potentials by wavelet decomposition. Brain Cogn 1995; 27:398–438

9. Stockmanns G, Nahm W, Petersen J, Thornton C, Kochs HD: Wavelet analysis of acoustically evoked potentials during repeated propofol sedation. Biomed Tech (Berl) 1997; 42(Suppl):373–4

10. Petersen J, Stockmanns G, Nahm W: EEG analysis for assessment of depth of anaesthesia, Fuzzy Systems in Medicine. Edited by Szczepaniak S, Lisboa P, Kacprzyk J. Berlin, Physica-Verlag, 2000, pp 261–77

11. Stockmanns G, Kochs E, Nahm W, Thornton C, Kalkman CJ: Automatic analysis of auditory evoked potentials by means of wavelet analysis, Memory and Awareness in Anaesthesia. Edited by Jordan C, Vaughan DJA, Newton DEF. Cambridge, Imperial College Press, 2000, pp 117–31

12. Smith WD, Dutton RC, Smith NT: Measuring the performance of anesthetic depth indicators. ANESTHESIOLOGY 1996; 84:38–51

13. Thornton C, Sharpe RM: Evoked potentials in anaesthesia. Br J Anaesth 1998; 81:771–81

14. Schwender D, Klasing S, Madler C, Pöppel E, Peter K: Depth of anesthesia: Midlatency auditory evoked potentials and cognitive function during general anesthesia. Int Anesthesiol Clin 1993; 31:89–106

15. Jones JG: Memory of intraoperative events. BMJ 1994; 309:967–8

16. Gajraj RJ, Doi M, Mantzaridis H, Kenny GN: Analysis of the EEG bispectrum, auditory evoked potentials and the EEG power spectrum during repeated transitions from consciousness to unconsciousness. Br J Anaesth 1998; 80:46–52

17. Thornton C, Heneghan CP, James MF, Jones JG: Effects of halothane or enflurane with controlled ventilation on auditory evoked potentials. Br J Anaesth 1984; 56:315–23

18. Schwender D, Klasing S, Madler C, Pöppel E, Peter K: Midlatency auditory evoked potentials and purposeful movements after thiopentone bolus injection. Anaesthesia 1994; 49:99–104

19. Dutton RC, Smith WD, Rampil IJ, Chortkoff BS, Eger EI 2nd: Forty-hertz midlatency auditory evoked potential activity predicts wakeful response during desflurane and propofol anesthesia in volunteers. ANESTHESIOLOGY 1999; 91:1209–20

20. Schwilden H, Stoeckel H: Investigations on several EEG-parameters as indicators of the state of anaesthesia the median: A quantitative measure of the depth of anaesthesia. Anaesth Intensivther Notfallmed 1980; 15:279–86

21. Rampil IJ, Matteo RS: Changes in EEG spectral edge frequency correlate with the hemodynamic response to laryngoscopy and intubation. ANESTHESIOLOGY 1987; 67:139–42

22. Sebel PS, Lang E, Rampil IJ, White PF, Cork R, Jopling M, Smith NT, Glass

PS, Manberg P: A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. Anesth Analg 1997; 84:891–9

23. Rampil IJ: A primer for EEG signal processing in anesthesia. ANESTHESIOLOGY 1998; 89:980–1002

24. Akay M: Wavelets in biomedical engineering. Ann Biomed Eng 1995; 23:531–42

25. Bertrand O, Bohorquez J, Pernier J: Time-frequency digital filtering based on an invertible wavelet transform: An application to evoked potentials. IEEE Trans Biomed Eng 1994; 41:77–88

26. Trejo LJ, Shensa MJ: Feature extraction of event-related potentials using wavelets: An application to human performance monitoring. Brain Lang 1999; 66:89–107

27. Wickerhauser MV: The discrete wavelet transformation, Adaptend Wavelet Analysis from Theory to Software. Edited by Peters KA. Cambridge, Wellesley-Cambridge Press, 1994, pp 213–36

28. Strang G, Nguyen T: Wavelets and Filterbanks. Wellesley, Wellesley-Cambridge Press, 1996

29. Daubechies I: Orthonormal bases of wavelets and multiresolution analysis, Ten Lectures on Wavelets. Edited by Daubechies I. Philadelphia, SIAM, 1992, pp 129–66