Forty-hertz Midlatency Auditory Evoked Potential Activity Predicts Wakeful Response during Desflurane and Propofol Anesthesia in Volunteers

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Background: Suppression of response to command commonly indicates unconsciousness and generally occurs at anesthetic concentrations that suppress or eliminate memory formation. The authors sought midlatency auditory evoked potential indices that successfully differentiated wakeful responsiveness and unconsciousness.

Methods: The authors correlated midlatency auditory evoked potential indices with anesthetic concentrations permitting and suppressing response in 22 volunteers anesthetized twice (5 days apart), with desflurane or propofol. They applied stepwise increases of 0.5 vol% end-tidal desflurane or 0.5 μg/ml target plasma concentration of propofol to achieve sedation levels just bracketing wakeful response. Midlatency auditory evoked potentials were recorded, and wakeful response was tested by asking volunteers to squeeze the investigator's hand. The authors measured latencies and amplitudes from raw waveforms and calculated indices from the frequency spectrum and the joint time-frequency spectrogram. They used prediction probability (P_K) to rate midlatency auditory evoked potential indices and concentrations of end-tidal desflurane and arterial propofol for prediction of responsiveness. A P_K value of 1.00 means perfect prediction and a P_K of 0.50 means a correct prediction 50% of the time (*e.g.*, by chance).

Results: The ~40-Hz power of the frequency spectrum predicted wakefulness better than all latency or amplitude indices, although not all differences were statistically significant. The P_K values for ~40-Hz power were 0.96 during both desflurane and propofol anesthesia, whereas the P_K values for the best-performing latency and amplitude index, latency of the Nb wave, were 0.86 and 0.88 during desflurane and propofol ($P = 0.10$ for ~40-Hz power compared with Nb latency), and for the next highest, latency of the Pb wave, were 0.82 and 0.84 ($P < 0.05$). The performance of the best combination of amplitude and latency variables was nearly equal to that of ~40-Hz power. The ~40-Hz power did not provide a significantly better prediction than anesthetic concentration; the P_K values for concentrations of desflurane and propofol were 0.91 and 0.94. Changes of ~40-Hz power values of 20% (during desflurane) and 16% (during propofol) were associated with a change in probability of nonresponsiveness from 50% to 95%.

Conclusions: The ~40-Hz power index and the best combination of amplitude and latency variables perform as well as predictors of response to command during desflurane and propofol anesthesia as the steady-state concentrations of these anesthetic agents. Because clinical conditions may limit measurement of steady-state anesthetic concentrations, or comparable estimates of cerebral concentration, the ~40-Hz power could offer advantages for predicting wakeful reponsiveness. (Key words: Anesthetic depth; arousal; attention; awareness; memory.)

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MIDLATENCY auditory evoked potentials (MLAEPs) may predict suppression of response to command and memory formation during anesthesia.[1-6] Absence of response to command is important because it implies an anesthetic effect in excess of that required to cause amnesia,[7-11] and the return of responsiveness heralds the impending return of a capacity for memory forma-

tion.[12-16] So, an indicator that predicts responsiveness could guide the administration of anesthetic agents, especially if neuromuscular blocking agents suppress a patient's ability to signal undesired awareness.

Anesthetic concentration is a highly predictive indicator of responsiveness; the awake minimum alveolar concentration (MAC_{Awake}) and its equivalent plasma concentration ($Cp_{50Awake}$) of an agent define the concentration at the 0.50 probability of wakeful response.[17,18] In clinical practice, anesthesia results from the sum of effects of several agents, and therefore a neurophysiologic indicator of responsiveness for a variety of anesthetic regimens would be useful. Several variables derived from the MLAEP have been examined to assess the correlation with responsiveness or memory formation: latency of the Nb peak,[1,2,5] amplitude of the Nb peak,[6] latencies of the Na and Pa peaks,[3,4] auditory evoked potential index,[19] variables derived from the frequency spectrum[4,20,21] or the joint time–frequency spectrogram,[21] and wavelet analysis.[22] The 40-Hz steady-state potential[23-25] and the "coherent" frequency, a frequency of steady-state stimulation evoking a maximum power response,[26] also have been evaluated.

In the present study, we examined several MLAEP frequency spectrum indices, in addition to conventional MLAEP latency and amplitude indices, and compared such indices against anesthetic concentration. To measure and compare the prediction accuracy of such a variety of possible indicators, some of which may be other than linearly scaled, we used a nonparametric statistical test, prediction probability (P_K).[27,28] We used P_K to identify the best-performing MLAEP index and then determined the specific values of this index that could be used to guide the administration of anesthesia by calculating the relation between the index and the probability of nonresponse to command.

Methods

Recruitment and Anesthesia Techniques

We enrolled 22 healthy male volunteers aged 21–30 yr with their informed consent and approval from the University of California, San Francisco, Committee on Human Research. Details of patient recruitment, anesthetic technique, and wakeful response testing have been described previously.[18] Each volunteer was anesthetized twice, once with desflurane (Baxter Pharmaceutical Products Division, Liberty Corner, NJ) and once with a continuous intravenous solution of propofol (Stuart

Pharmaceuticals, Wilmington, DE). Order of anesthetic administration was randomized, with 5 days between administrations. Each drug was delivered in concentration steps maintained for 15 min.

Desflurane administration began with a single-step increase to an end-tidal concentration of 2.0%, as determined by a respiratory gas analyzer (Capnomac, Datex, Helsinki, Finland) calibrated using secondary (cylinder) standards. Volunteers were tested for responsiveness as defined by their response to a verbal request to squeeze an investigator's hand one, two, or three times. Desflurane end-tidal concentration was increased step-wise, 0.5 vol%, at 15-min intervals until the volunteer failed to respond appropriately. MAC_{Awake} for each volunteer equaled the mean of the concentrations just permitting and preventing appropriate response to command.[17] For the final concentration step, end-tidal desflurane concentration was increased to 1.5 or 2.0 times MAC_{Awake} for that volunteer.

For volunteers receiving propofol, intravenous delivery of propofol from a syringe pump (Ohmeda 9000, Ohmeda, Madison, WI) was computer-controlled using an infusion rate–time profile[29] to deliver targeted step increases of arterial propofol, beginning with a single-step increase to a target concentration of 1.5 μg/ml, after which concentration was increased step-wise 0.5 μg/ml at 15-min intervals until the volunteer did not respond appropriately to the hand-squeeze request. For each volunteer, $Cp50_{Awake}$ (analogous to MAC_{Awake}) was calculated as the mean of the target concentrations just permitting and preventing appropriate response to command. For the final concentration step, target propofol concentration was increased to 1.5 or 2.0 times $Cp50_{Awake}$ for each volunteer. We determined propofol concentrations in heparinized arterial blood samples withdrawn from the left radial artery. The samples were analyzed with high-performance liquid chromatography using the technique of Plummer.[30]

Midlatency Auditory Evoked Potentials

After abrading the skin (OmniPrep, DO Weaver, Denver, CO), silver–silver chloride electrodes were placed at the vertex (active), on both mastoids (reference), and overlying the right clavicle (ground). Contact impedance differed by less than 2 kΩ between electrodes. A Pathfinder I (Nicolet Instruments, Madison, WI) was used for acoustic stimulation and recording of MLAEPs. A 150-μs unidirectional rectangular wave pulse provided a binaural rarefraction click at 80 dB with a frequency of 9.3 Hz *via* acoustically shielded headphones (Telephonics TDH

39P, Huntington, NY). MLAEPs were recorded from 0 to 100 ms (512 data points) using a 15- to 1,500-Hz bandpass filter. Individual trials with response signal >90% of amplifier voltage limit were automatically rejected as artifacts. The average from 1,000 stimulations obtained over a 2- to 3-min period provided the MLAEP.

We recorded one, two, or three MLAEPs 9 min after each 0.5% or 0.5 μg/ml step increase. Volunteers were tested for responsiveness after recording MLAEPs.

Further MLAEP analysis was conducted on a Macintosh computer (Apple Computer, Cupertino, CA). If replicated MLAEPs were available, we averaged the MLAEPs to obtain a single waveform and used that single waveform for subsequent data analysis. We defined the waveform occurring just before loss of responsiveness as Resp, that occurring just after loss of responsiveness as NoResp, and that occurring 1.5-2.0 times MAC_{Awake} (or $Cp50_{Awake}$) as $NoResp_{next}$. For each volunteer and anesthetic agent, we defined a waveform set as the Resp, NoResp, and $NoResp_{next}$ waveforms.

For each MLAEP waveform, we calculated MLAEP power spectrum indices using joint time–frequency analysis (JTFA)[31] (LabVIEW, National Instruments, Austin, TX), using the short-time Fourier transform and a Hanning window. We used JTFA because the standard Fourier transform–based methods of measuring the MLAEP frequency spectrum usually incorporate a "window" function[32] that accentuates information at the center latency of the MLAEP sweep (e.g., 50 ms of a 100-ms duration acquisition). Because maximally predictive information may be in frequency spectra calculated with nonstandard windowing, we used JTFA to vary the latency of the window center. Like standard Fourier transform–based methods, JTFA measures power as a function of frequency, and in addition as a function of window-center latency. After appropriate scaling, the JTFA calculated the two-sided power density spectrum, also sometimes termed power spectra, in microvolts squared per hertz (μV^2/Hz), for a range of windows centering at specified latencies; for a window center at 50 ms, the width of the window at half power was ± 18 ms and the frequency width was ± 7 Hz. The JTFA used zero padding to 200 ms to obtain a frequency spacing of 5 Hz. For each MLAEP waveform, we calculated power density spectra for windows centered from 20-74 ms, at 3-ms intervals. Then, for each of these power density spectra, we measured power density over the range from 20-80 Hz, at 5-Hz intervals, to obtain indices of power density at each frequency bin and latency interval (e.g., $Pwr_{40-Hz38\ ms}$).

To compare our JTFA results with more conventional fast Fourier transform (FFT) analysis, we used Acq-Knowledge (ver. 3.0, BIOPAC Systems, Goleta, CA) to calculate power density at 40 Hz. The FFTs were calculated using a standard Hanning window, centered at 50 ms, and zero padding was added to extend the epoch to 200 ms. After appropriate scaling, the two-sided power density of each FFT spectrum was measured in microvolts squared per hertz (μV^2/Hz) at 40 Hz to create an index we termed $Pwr_{FFT40-Hz}$.

To compare the predictive performance of these MLAEP power indices with that of standard MLAEP latency and amplitude indices, we measured latency and amplitude values using AcqKnowledge for each MLAEP. The waveforms were passed through a 511-coefficient Finite Impulse Response (FIR) highpass filter with Blackman -61-dB windowing and a -6-dB cutoff at 15 Hz. We identified the MLAEP peaks by simultaneously displaying all three waveforms of a volunteer's set and then selecting peaks according to the expected latency (e.g., the Na peak was the maximum negative voltage between 17 and 22 ms) and the similarity in appearance of the peaks among the three waveforms, considering the tendency for peak latency to progressively increase from Resp to NoResp to $NoResp_{next}$. Latency was measured from stimulus presentation to the peak voltages (e.g., Nb) to create MLAEP indices (e.g., Lat_{Nb}).[33] Amplitude was measured from the zero-voltage baseline to the peaks (e.g., Nb to create Amp_{Nb}). We also calculated the peak-to-peak voltage of $Amp_{Pa} - (Amp_{Na} + Amp_{Nb})/2$ to create Amp_{NaPaNb}.[34]

After finding that Lat_{Nb} was the best-performing latency index and Amp_{NaPaNb} the best-performing amplitude index, and hypothesizing that these indices contained independently predictive information, we combined Lat_{Nb} and Amp_{NaPaNb} into a new single-number index:

$$Lat_{Nb}Amp_{NaPaNb} = Lat_{Nb}(ms) - \frac{Amp_{NaPaNb}(\mu V)}{10}.$$

Groups

In preparation for statistical analysis, for each anesthetic, we created a response group that consisted of pooled Resp waveforms, and a no-response group that consisted of the pooled NoResp and $NoResp_{next}$ waveforms. We called the combined response and no-response groups for each anesthetic the complete group for that anesthetic. Because the MLAEP waveforms of some volunteers were missing or appeared artifactual

(which might unfairly degrade predictive performance), we created an extended group for each anesthetic by selecting from the complete group the two thirds (14 of 21) of the volunteers having complete sets of waveforms that were relatively free of artifacts. We also created a bracketed group for each anesthetic, containing the MLAEPs that just bracketed wakeful response (*i.e.*, Resp and NoResp waveforms in the extended group and excluding $NoResp_{next}$ waveforms).

Statistical Analysis

We used $P_K{}^{27,28}$ to calculate predictive performances of MLAEP and concentration indices. For example, consider two randomly selected Nb latency values, one a Resp and one a NoResp. The P_K is the probability that the Nb latency values correctly predict which waveform is the Resp and which is the NoResp. A P_K of 0.50 means that the index correctly predicts responsiveness 50% of the time (*e.g.*, by chance) and a P_K of 1.00 implies that the index predicts responsiveness perfectly.

Having calculated a large array of spectral power densities over a range of frequency bins and latency intervals, we sought to determine the optimum frequency and latency for separating responding and nonresponding volunteers. To do so, we calculated the P_K values at each frequency bin and latency interval for each anesthetic and then examined topographic surfaces of P_K as a function of frequency and latency to identify the peak in P_K values; the optimum frequency and latency values were defined as those corresponding to the P_K peak.

We also used P_K to compare predictive performance of MLAEP and concentration indices, for each database. To compare the P_K value of each MLAEP index with the P_K value of the corresponding desflurane or propofol concentration, we calculated the difference and statistical significance of the difference at the $P = 0.05$ and 0.01 criteria levels (two-tail test, no Bonferroni correction). For each MLAEP index, we also calculated the statistical significance of the difference for predictions of desflurane and propofol groups combined. To do so, we pooled the P value of the difference during desflurane anesthesia with that during propofol anesthesia to calculate a product that has a chi-square–like distribution, and then we tested the significance at the $P = 0.05$ and 0.01 criteria levels.[35] We also compared the predictive performance of the best-performing MLAEP power indices with that of the MLAEP latency and amplitude indices by similarly calculating differences between P_K values and the statistical significances of the differences.

To calculate specific indicator values for predicting a volunteer's probability of nonresponsiveness, we applied logistic regression analysis[36] (SPSS, Chicago, IL) to each extended group to calculate the probability of wakeful response as a function of indicator value. Logistic regression analysis provided β, a measure of the steepness (slope) of the logistic regression curve, and $Indicator_{50}$ and $Indicator_{95}$, the values of the indicators at which the probability of nonresponse equals 0.50 and 0.95.[37] Before applying logistic regression analysis, we appropriately transformed indicator scales[27,38] (see Appendix). We calculated logistic regressions for anesthetic concentrations, $Pwr_{40-Hz38ms}$, $Pwr_{40-Hz50ms}$, and Lat_{Nb}. To display logistic regression curves for these indices over comparable value ranges, we calculated linear regressions of $Pwr_{40-Hz38\ ms}$ and Lat_{Nb} against $\log_{10}$(concentration), for desflurane and propofol.

Results

Twenty-one volunteers received desflurane and 22 received propofol (one volunteer did not complete the desflurane portion of the study because of a respiratory infection). Figure 1 is a representative illustration of the progressive increase in latency and decrease in amplitude with decreasing responsiveness in a volunteer receiving propofol. Most sets showed a similar pattern of change between Resp and NoResp, but two sets showed no change, and one set showed a reversed change (decreased latency and increased amplitude). Figure 1 also shows the FFT power density spectra of the MLAEPs from the volunteer receiving propofol. Multiple MLAEPs for a given volunteer, averaged to create a single MLAEP for that volunteer, were frequently recorded at the $NoResp_{next}$ level (13 of 21 desflurane volunteers, 15 of 22 propofol volunteers) but infrequently at the Resp level (1 of 21 desflurane, 1 of 22 propofol) and NoResp level (0 of 21 desflurane, 1 of 22 propofol).

Figure 2 shows the JTFA spectrograms of the MLAEPs shown in figure 1.

Figures 3 and 4 show all the MLAEP waveforms in the response and no-response groups of the desflurane and the propofol extended groups.

Optimal Latency and Frequency for Calculating Pwr_{40-Hz}

Figure 5 shows topographic maps of P_K values for power density over the latency range of 20–74 ms and the frequency range of 25–60 Hz for desflurane and propofol, for the bracketed groups. The P_K values

A Auditory Evoked Potentials
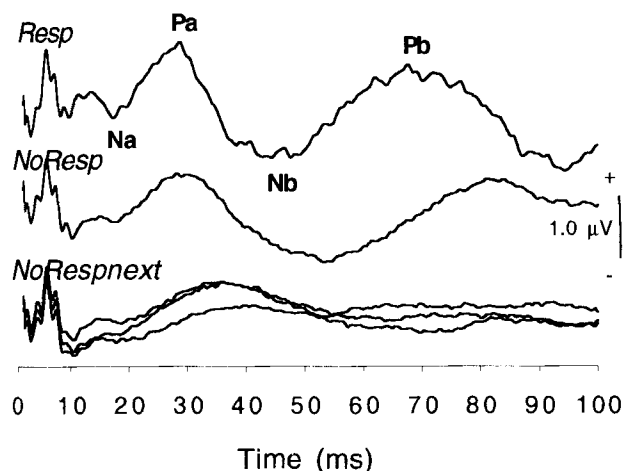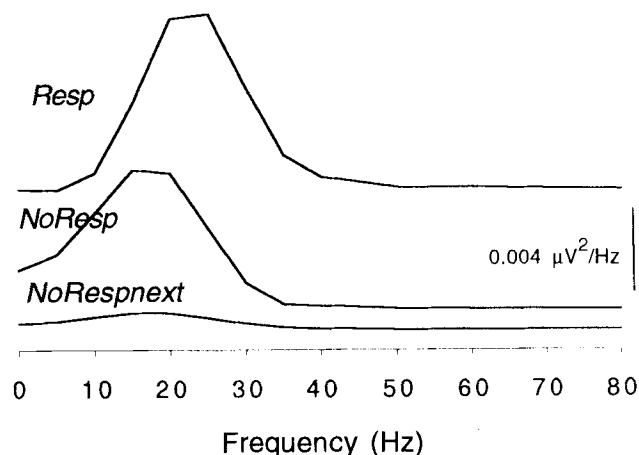
B Power Spectra

Fig. 1. A set of midlatency auditory evoked potential waveforms from one volunteer during propofol, showing the change in appearance of the waveforms (A) and the power density spectra (B) from Resp to NoResp to NoResp$_{next}$. (Three replicated NoResp$_{next}$ waveforms are shown here before being averaged to obtain the single waveform).

peaked in the region of 38 ms and 40-45 Hz for desflurane, and 50 ms and 40-45 Hz for propofol. The P_K values for the extended groups peaked at the same latencies and frequencies as the corresponding bracketed groups. The P_K values for these highest performing

Fig. 2. The joint time–frequency analysis results for the set of midlatency auditory evoked potential waveforms shown in figure 1. The vertical axis is power density and the horizontal axes are frequency and window center latency (see text). The bold lines are the power density spectra with window-center latencies of 50 ms and correspond to the power density spectra shown in figure 1B.

power density indices were 0.96 ± 0.03 (P_K value $\pm$ SE) for Pwr$_{40-Hz38\ ms}$ during desflurane (table 1), and 0.96 ± 0.02 for Pwr$_{40-Hz50\ ms}$ during propofol. We term these indices Pwr$_{40-Hz}$.

Comparison of Prediction Performance

The alternative ~40-Hz indicator calculated using a conventional FFT, Pwr$_{FFT40-Hz}$, had nearly the same high level of performance as Pwr$_{40-Hz}$ (table 1). (Comparisons of P_K values must be made within a response-no-response group pair, i.e., within the desflurane column or the propofol column.[27])

The P_K value for concentration of desflurane was 0.91 ± 0.05 (table 1) and for measured propofol was 0.94 ± 0.03. The P_K values for Pwr$_{40-Hz}$ indices were not greater than those for corresponding concentrations, at $P = 0.05$. •

The P_K values for all MLAEP latency or amplitude indices in the extended groups were less than for corresponding concentrations of desflurane and propofol (table 1), although not all differences achieved statistical significance at $P = 0.05$. Of the latency and amplitude indices, Lat$_{Nb}$ had the highest prediction performance: $P_K = 0.86 \pm 0.06$ during desflurane and 0.88 ± 0.06 during propofol. The P_K values for Pwr$_{40-Hz}$ compared with P_K values for Lat$_{Nb}$ yielded $P = 0.16$ during desflurane anesthesia, $P = 0.14$ during propofol anesthesia, and pooled $P = 0.10$ for groups combined. The P_K values for Pwr$_{40-Hz}$ compared with those for the next
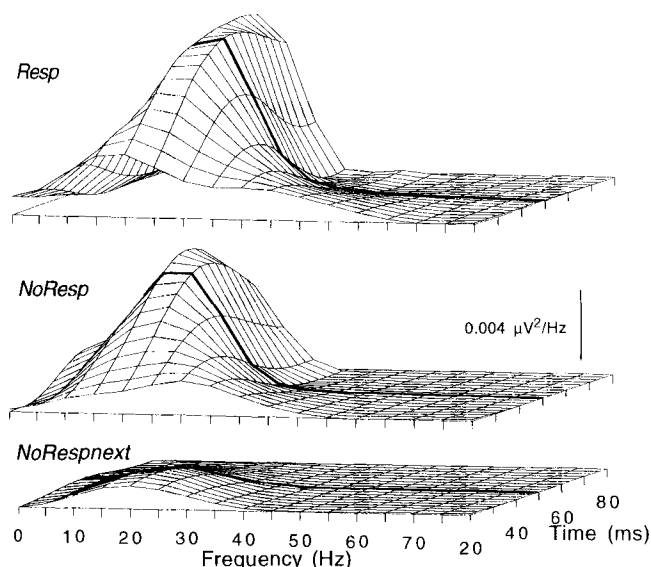
Response Group, Desflurane
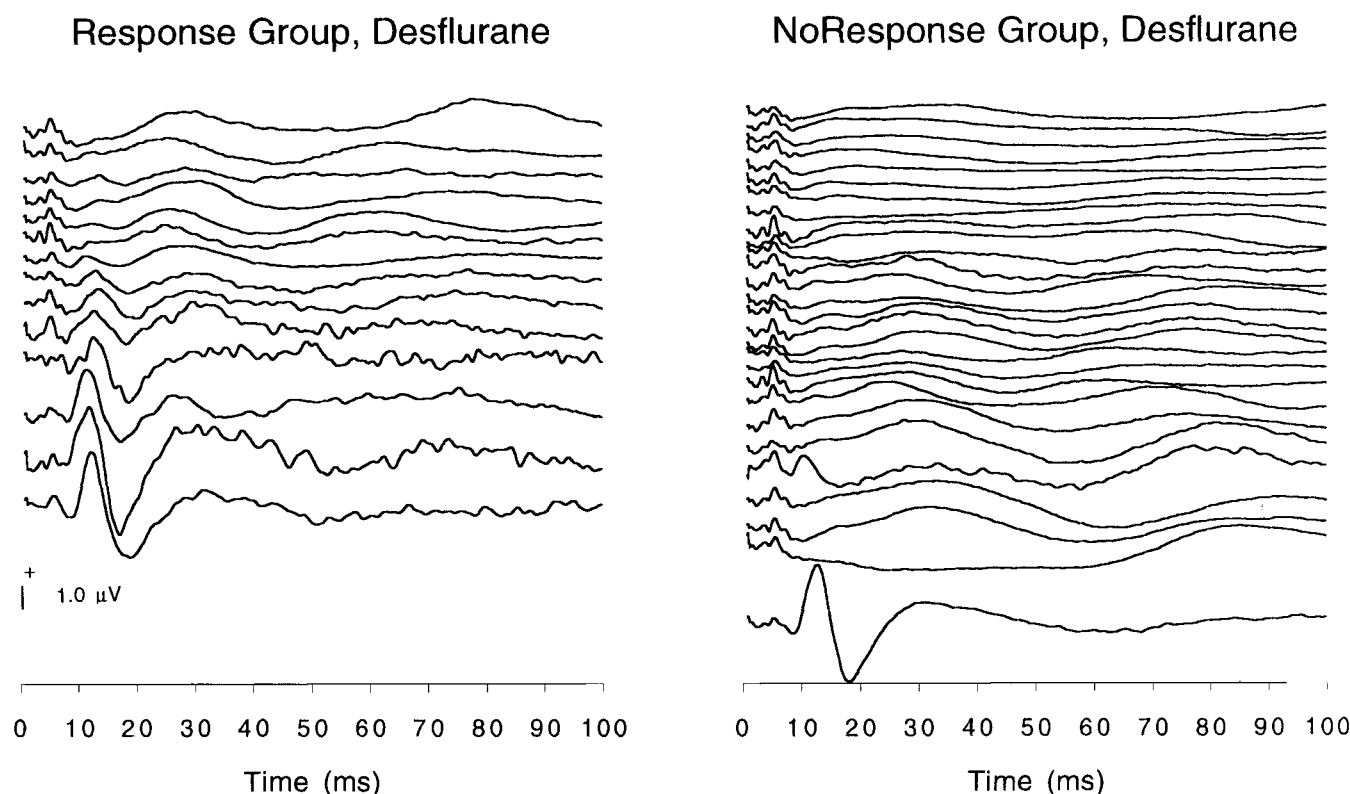
NoResponse Group, Desflurane

Fig. 3. All the waveforms in the response group (Resp) and no-response group (NoResp and NoResp$_{next}$) of the desflurane extended group. The waveforms are ordered by overall similarity of latencies and amplitudes.

best-performing latency and amplitude index, Lat$_{Pb}$, yielded pooled $P < 0.05$.

Combining the best latency index, Lat$_{Nb}$, and amplitude index, Amp$_{NaPaNb}$, into a composite single-number index, Lat$_{Nb}$Amp$_{NaPaNb}$, improved prediction; $P_K = 0.95 \pm 0.03$ during desflurane and 0.93 ± 0.04 during propofol.

For the bracketed group, the P_K values for concentration and for all MLAEP indices decreased compared with their corresponding values in the combined groups. (Like other measures of correlation, P_K is sensitive to data range. By deleting Resp$_{next}$, the data range decreased for all indices, and thus all P_K values would also be expected to decrease.[27]) The P_K value for desflurane was 0.82 ± 0.09 and for propofol was 0.88 ± 0.06. The corresponding P_K value for Pwr$_{40\text{-Hz}38 \text{ ms}}$ was 0.91 ± 0.06 and for Pwr$_{40\text{-Hz}50 \text{ ms}}$ was 0.92 ± 0.05. The P_K values for these Pwr$_{40\text{-Hz}}$ indices compared with P_K values for concentration were not significantly different, yielding $P = 0.44$ during desflurane anesthesia, $P = 0.44$ during propofol anesthesia, and pooled $P = 0.50$ for

groups combined. For Lat$_{Nb}$, the corresponding P_K values were 0.81 ± 0.08 and 0.81 ± 08.

Logistic Regression Analysis

Table 2 shows the logistic regression analysis results for concentration, Pwr$_{40\text{-Hz}38 \text{ ms}}$, Pwr$_{40\text{-Hz}50 \text{ ms}}$, and Lat$_{Nb}$, in terms of the values of Indicator$_{50}$, Indicator$_{95}$, and β slope[37] for the extended groups. The Indicator$_{50}$ value, analogous to MAC$_{Awake}$, for concentration of desflurane was 2.45 ± 0.11 vol% and of propofol was 2.55 ± 0.10 μg/ml, consistent with previously published results.[18] The Indicator$_{50}$ value for Pwr$_{40\text{-Hz}38 \text{ ms}}$ during desflurane was -3.36 ± 0.11 log$_{10}(\mu V^2/Hz)$ and during propofol was -3.28 ± 0.09 log$_{10}(\mu V^2/Hz)$. The Indicator$_{95}$ value, analogous to MAC$_{Awake05}$, for Pwr$_{40\text{-Hz}38 \text{ ms}}$ during desflurane was -4.02 ± 0.25 log$_{10}(\mu V^2/Hz)$ and during propofol was -3.80 ± 0.19 log$_{10}(\mu V^2/Hz)$. Consistent with the P_K values in table 1, during desflurane anesthesia, the slope for Pwr$_{40\text{-Hz}38 \text{ ms}}$ was steeper than that for Pwr$_{40\text{-Hz}50 \text{ ms}}$; during propofol anesthesia, the slope for Pwr$_{40\text{-Hz}50 \text{ ms}}$ was steeper than for Pwr$_{40\text{-Hz}38\text{-ms}}$.

Response Group, Propofol

+
| 1.0 µV
-

0 10 20 30 40 50 60 70 80 90 100

Time (ms)

NoResponse Group, Propofol

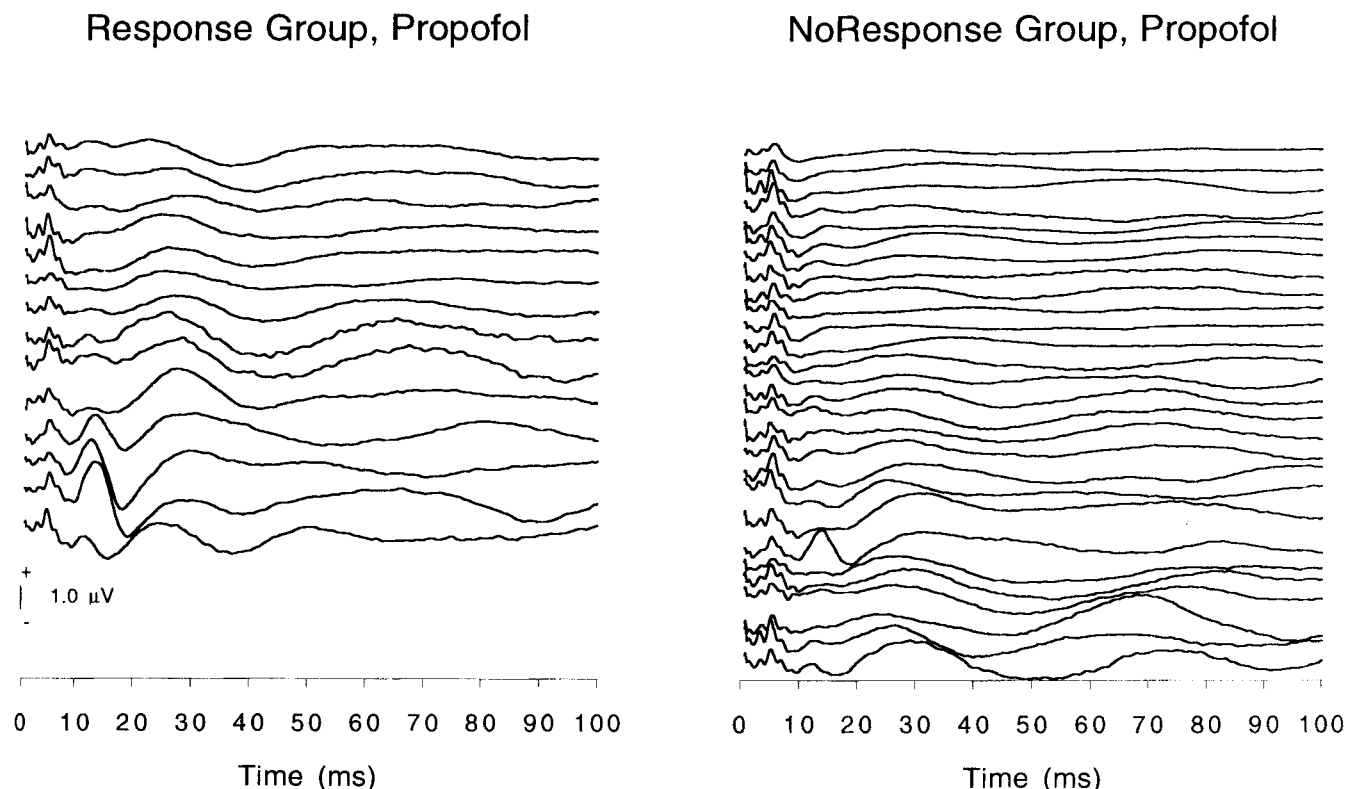0 10 20 30 40 50 60 70 80 90 100

Time (ms)

Fig. 4. All the waveforms in the response group and no-response group of the propofol extended group. The waveforms are ordered by overall similarity of latencies and amplitudes.

Figure 6 shows logistic regression curves for anesthetic concentration, $Pwr_{40\text{-Hz38 ms}}$, and Lat_{Nb} during desflurane and propofol. The curves graphically display results shown in table 2.[37] Although the prediction performance of an indicator is shown by the steepness of the slope of the curve, because of the assumptions used for scaling indices and determining comparable value ranges, we did not attempt to compare differences between the curves.

As calculated from $Indicator_{50}$ and $Indicator_{95}$ in table 2, for $Pwr_{40\text{-Hz38 ms}}$ a change of nonresponsiveness from 50 to 95% was associated with a change of 0.66 $\log_{10}(\mu V^2/Hz)$ during desflurane (a 20% change from the $Indicator_{50}$ value) and 0.52 $\log_{10}(\mu V^2/Hz)$ during propofol (a 16% change).

Discussion

Although many MLAEP features have been proposed as indicators of wakeful responsiveness, few comparisons of the predictive performances of these indicators have been made. Such comparisons constitute one of the

primary contributions of the present work, and P_K allows such comparisons.[27,28] We found that the best-performing indicators were the ~40-Hz power ($Pwr_{40\text{-Hz}}$), a composite Nb latency and NaPaNb amplitude index ($Lat_{Nb}Amp_{NaPaNb}$), and Nb latency (Lat_{Nb}) .

After finding good predictive performance of ~40-Hz power measured by the JTFA spectrogram, we confirmed that a more conventional FFT analysis of ~40-Hz power of the MLAEP provided similar high performance.

We found that 40–45 Hz was the range of the optimal frequency of the MLAEP power for predicting response to command. This finding confirms previous reports associating ~40-Hz activity and wakefulness.[4,26,39–48] The optimal latency for measuring the MLAEP power was 38 ms during desflurane and 50 ms during propofol. These latency values were obtained by inspecting the topographic surfaces of P_K values (fig. 5). We did not attempt to calculate the confidence limits of these values. Inspection and comparison of individual power density spectra suggest that the difference in these latency values would not be statistically significant.

Figure 6 provides an example of specific ~40-Hz ac-
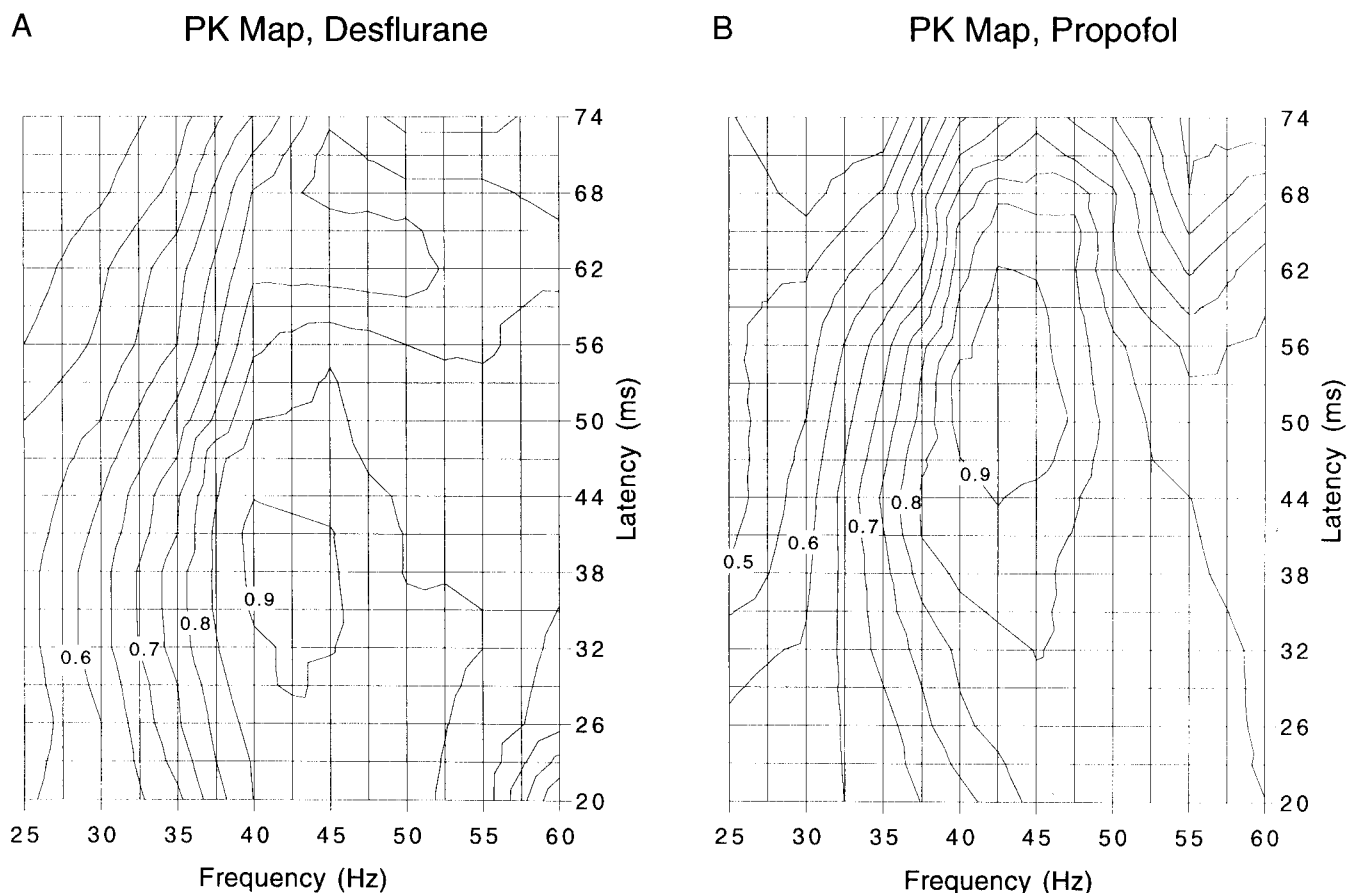
A PK Map, Desflurane

B PK Map, Propofol

Fig. 5. Topographic map of prediction probability (P_K) values over the latency range of 20–74 ms and frequency range of 25–60 Hz for the desflurane bracketed group (*A*) and the propofol bracketed group (*B*). The P_K values during desflurane administration plateau at 38 ms and 40–45 Hz, and P_K values during propofol administration plateau at 50 ms and 40–45 Hz.

tivity values that could be used to guide the administration of anesthesia.

Of the latency and amplitude indices, Lat_{Nb} had the highest prediction performance, validating previous reports about the efficacy of this index.[1,2,5,22,49] The Lat_{Nb} did not predict as well as anesthetic concentration, although the differences were not statistically significant. In contrast, Tooley *et al.*[49] reported that Nb latency predicted eyelash response better than concentration of propofol.

Combining Lat_{Nb} and Amp_{NaPaNb} into a new single-number index, $Lat_{Nb}Amp_{NaPaNb}$, improved predictive performance slightly. To create the formula for calculating $Lat_{Nb}Amp_{NaPaNb}$, we calculated P_K values for alternative combinations of Lat_{Nb} and Amp_{NaPaNb} and found that the best performance was by a formula summing the increase in latency (in microseconds) of Lat_{Nb} and decrease in amplitude (in microvolts) of Amp_{NaPaNb}, in which amplitude was normalized by a factor of 10 so

that latency and amplitude had equally weighted changes over the concentration ranges.

It would be of interest to compare the 40-Hz auditory steady-state response (ASSR) with the ~40-Hz power of the MLAEP. Although Plourde and Villemure[50] compared the ASSR with latency and amplitude indices of the MLAEP, the ~40-Hz· activity of the MLAEP was not reported. Compared with the ~40-Hz power of the MLAEP, the ASSR and the coherent frequency may have advantages as predictors because, for an individual subject, the optimum stimulus frequency for evoking the response could be determined while a subject was awake, and the magnitude of that optimum response used to normalize the values during anesthesia.[24-26,39,40] In contrast, MLAEP is measured using a fixed, relatively slow stimulus rate, 9.3 Hz for example, which may not be optimal for the inherent response of all individuals. Individualization for response frequency may be important because, although the optimum frequency of audi-

Table 1. Prediction Probability Values for Anesthetic Concentrations and Midlatency Auditory Evoked Potential ~40-Hz Power, Latency, and Amplitude Indices for the Extended Groups

	Desflurane	Propofol
Concentration	0.91 ± 0.05	0.94 ± 0.03
$Pwr_{40-Hz38\ ms}$	0.96 ± 0.03	0.93 ± 0.04
$Pwr_{40-Hz50\ ms}$	0.92 ± 0.04	0.96 ± 0.02
$Pwr_{FFT40-Hz}$	0.91 ± 0.05	0.96 ± 0.02
Lat_{Na}	0.79 ± 0.07	$0.71 \pm 0.08^{**}\ddagger$
Lat_{Pa}	$0.77 \pm 0.07^{*}$	$0.70 \pm 0.08^{**}\ddagger$
Lat_{Nb}	0.86 ± 0.06	0.88 ± 0.06
Lat_{Pb}	0.82 ± 0.07	0.84 ± 0.07
Amp_{Na}	0.85 ± 0.06	$0.71 \pm 0.10^{*}\dagger$
Amp_{Pa}	0.78 ± 0.07	$0.78 \pm 0.08^{*}\dagger$
Amp_{Nb}	$0.61 \pm 0.09^{**}$	$0.81 \pm 0.08^{*}\ddagger$
Amp_{Pb}	$0.65 \pm 0.09^{*}$	$0.66 \pm 0.08^{**}\ddagger$
Amp_{NaPaNb}	0.80 ± 0.07	$0.87 \pm 0.05\dagger$
$Lat_{Nb}Amp_{NaPaNb}$	0.95 ± 0.03	0.93 ± 0.04

Data are P_K values $\pm$ SE. No ~40-Hz power values were greater than corresponding concentration values at $P = 0.05$.

$^{*} P < 0.05$, $^{**} P < 0.01$: value less than corresponding concentration value.

$\dagger P < 0.05$, $\ddagger P < 0.01$: pooled MLAEP value less than concentration value.

tory stimuli of a group of 16 awake subjects studied by ASSR was 40 Hz, the range was 20-50 Hz.[51] Similarly, the range of coherent frequency for a group of 10 awake subjects was 34-44 Hz.[40] After individualizing the ASSR stimulus, Plourde et al.[25] found that the predictive value for loss of consciousness by ASSR was the same as that by isoflurane concentration.

We created two groups to evaluate predictive performances, the extended group and the bracketed group. The extended groups consisted of one response (Resp) and two nonresponse (NoResp and NoResp$_{next}$) MLA-EPs, reflecting our interest in determining MLAEP indices that could identify patients emerging from deeper anesthetic levels to wakefulness. Although we created the extended group to provide a group for analysis that contained a complete set of waveforms for each volunteer and a reduced number of artifactual waveforms, even some waveforms in the extended groups appeared irregular and of marginally acceptable quality, as seen in figures 2 and 3.

We created the bracketed groups to enhance our ability to evaluate whether MLAEP indices could predict better than concentration, which would suggest a reflection of basic neurophysiologic mechanisms related to wakefulness. Bracketed groups were created by deleting

the NoResp$_{next}$ MLAEPs from the extended groups, decreasing the range of index values, and, as expected,[27] decreasing the P_K values of MLAEP and concentration indices. Although P_K values of ~40-Hz power exceeded those of anesthetic concentrations, the differences were not statistically significant. If we had found significantly higher P_K values for ~40-Hz power, this would have suggested that prediction performance by ~40-Hz power may not simply reflect concentration, and that ~40-Hz power may reflect basic neurophysiologic mechanisms related to wakeful response.

If ~40-Hz activity reflects mechanisms related to wakefulness, what might those mechanisms be? The brain generates gamma oscillations, also called ~40-Hz oscillations, although the oscillations may range from 20-90 Hz.[42] Gamma oscillations arise from the thalamocortical system and are modulated by the intralaminar nuclei of the thalamus, which are in turn influenced by the midbrain reticular activating system.[48,52] Although gamma oscillations may occur during anesthesia and non-rapid eye movement sleep, gamma oscillations markedly increase during rapid eye movement sleep, arousal, and awakening, occurring more frequently, increasing in amplitude, and becoming synchronous over widespread

Table 2. Values of the Indicator$_{50}$ and Indicator$_{95}$ and of β for Indicator-Response Logistic Regression Curves for the Extended Groups

	Desflurane	Propofol
Concentration (vol%, $\mu g/ml$)		
Indicator$_{50}$	2.45 ± 0.11	2.55 ± 0.10
Indicator$_{95}$	3.24 ± 0.34	3.18 ± 0.28
β (Log$_{10}$)	23.6 ± 5.0	29.7 ± 8.6
$Pwr_{40-Hz38\ ms}$ (Log$_{10}(\mu V^2/Hz)$)		
Indicator$_{50}$	-3.36 ± 0.11	-3.28 ± 0.09
Indicator$_{95}$	-4.02 ± 0.25	-3.80 ± 0.19
β	-4.38 ± 1.57	-5.75 ± 1.97
$Pwr_{40-Hz50\ ms}$ (Log$_{10}(\mu V^2/Hz)$)		
Indicator$_{50}$	-3.71 ± 0.14	-3.64 ± 0.08
Indicator$_{95}$	-4.55 ± 0.30	-4.07 ± 0.16
β	-3.46 ± 1.12	-7.04 ± 2.44
Lat_{Nb} (ms)		
Indicator$_{50}$	48.5 ± 1.6	43.8 ± 1.2
Indicator$_{95}$	59.8 ± 3.6	52.3 ± 3.0
β	0.26 ± 0.09	0.36 ± 0.07

Data are estimates $\pm$ SE.

Indicator$_{50}$ = indicator value at the nonresponse probability of 0.50; Indicator$_{95}$ = indicator value at the nonresponse probability of 0.95; and β = slope parameter of the logistic regression curve.
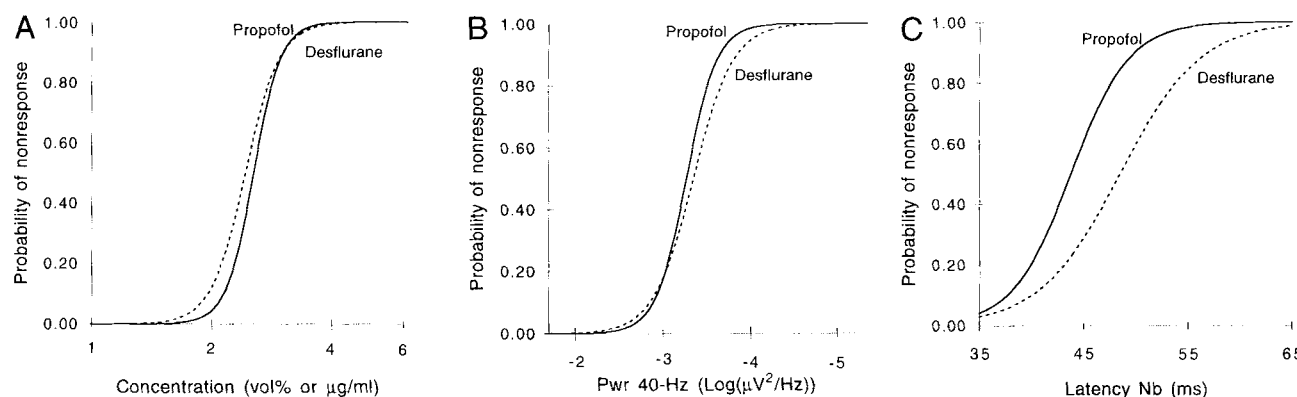
Fig. 6. Logistic regression analysis curves relating specific indicator values of anesthetic concentration (scaled as $\log_{10}$) (*A*), $Pwr_{40\text{-}Hz38\ ms}$ (*B*), and Lat_{Nb} to probability of nonresponse to command during desflurane and propofol (*C*). The range of $Pwr_{40\text{-}Hz38\ ms}$ values corresponds to ranges for desflurane of 1.0–6.0 vol% and for propofol of 0.7–7.0 µg/ml. The range of Lat_{Nb} values corresponds to ranges for desflurane of 1.0–6.0 vol% and for propofol of 1.0–10.0 µg/ml.

areas of the cerebral cortex.[41–47,53] In awake humans, auditory stimuli reset the synchronicity of gamma oscillations, producing coherent oscillations over the cortex.[41,43,44] Further investigation might reveal whether the ~40-Hz activity we measured from extracranial scalp electrodes is related to the gamma oscillations.

Although we speculate that ~40-Hz activity may reflect mechanisms related to wakeful response, ~40-Hz activity may not reflect the mechanism underlying responsiveness, because for three volunteers the ~40-Hz power of NoResp exceeded that of Resp. However, as discussed subsequently, a subject may not respond even though wakeful, and such a lack of response could help explain the reversed change in ~40-Hz power for these three volunteers. Also against the possibility that ~40-Hz power reflects the mechanism underlying wakefulness is the observation by Steriade *et al.*[46] that ~40-Hz synchronization of cortical electroencephalographic activity of awake cats disappeared and reappeared without a detectable reason, although wakefulness appeared to be uninterrupted.

We chose hand squeezing to demonstrate a volunteer's ability for cognitive processing and because failure to appropriately respond indicates probable suppression of memory formation.[7–16] We did not distinguish between a brief and a sustained duration of wakefulness, although this distinction may better indicate the potential for memory formation.[14,15] Occasionally, a person may be wakeful and yet not respond to command,[2,54] and this failure to respond might explain some cases in which MLAEP indices showed little or no change between Resp and NoResp (*i.e.*, the NoResp should then have been labeled a Resp). We did not choose eye opening on command as the endpoint of wakefulness[17] because eye opening may be an orienting or startle-like response instead of one that indicates cognitive processing.

There were other shortcomings in our methods that also could be avoided in future studies. Replicate MLAEPs (which increase confidence in the waveforms) were infrequently recorded because of time restraints. We studied volunteers during induction of anesthesia rather than emergence from anesthesia. If MLAEPs during emergence differ from those during induction (*i.e.*, hysteresis), our findings might not hold for emergence. Other reports suggest that hysteresis might not be a problem: Nb latency provides similar results during repeated transitions from consciousness to unconsciousness and back again.[5] Finally, we studied volunteers who did not receive noxious stimulation, such as surgical stimulation. Surgical stimulation can alter MLAEP waveforms, causing increased amplitude of the peaks.[55]

Although MLAEP indices did not predict significantly better than anesthetic concentration, electroencephalographic indices that performed well, such as ~40-Hz activity or bispectral index,[11,32] could offer advantages over anesthetic concentration. During clinical anesthesia, the usefulness of anesthetic concentration as a predictor is confined to the inhaled anesthetics, in which end-tidal concentrations can be measured on line. If intravenous agents contribute significantly to production of anesthesia, measurement of the concentration of inhaled agents does not suffice as an adequate predictor. Additional limitations result from changes in inhaled and intravenous agent delivery after which pharmacokinetics limit the capacity to estimate cerebral anesthetic concentrations. Thus, an electrophysiologic index that pre-

dicts wakefulness independent of these variables would be valuable, even though it does not necessarily predict significantly better than steady-state anesthetic concentration. Of note, at the present, the determination of MLAEP requires more technical expertise and effort than electroencephalographic (or bispectral index) monitoring.

In summary, of the MLAEP indices we studied, ~40-Hz power of the MLAEP frequency spectrum provided the highest prediction performance of wakeful responsiveness in volunteers receiving desflurane and propofol. The composite $Lat_{Nb}Amp_{NaPaNb}$ indices provided the next best performances, and Lat_{Nb} the third best. The ~40-Hz power is an objective measure that can be obtained from readily available instruments and may find clinical application for predicting wakeful responsiveness.

Appendix: Rescaling Indicator Values to Calculate Logistic Regression Curves

To appropriately apply logistic regression analysis, criteria about distribution of data need to be satisfied; if the criteria are not met, data may be transformed by nonlinear rescaling. To examine the appropriateness of the scaling of MLAEP indices, we compared the data points of each index with their corresponding logarithmically scaled concentration data points. We did so because logarithmically scaled concentration data meet the criteria and provide the best fit for constructing concentration–response logistic regression curves.[38] Scaling of MLAEP indices were compared with log_{10}(concentration) by visually examining x-y scatter plots for nonlinear trends and verifying improvements in indicator scale transformations by increases in correlation coefficients (r) found by comparing the transformed indicators with log_{10}(concentration). In this way, acceptable scaling was obtained with $log_{10}(Pwr_{40-Hz38\ ms})$, $log_{10}(Pwr_{40-Hz50\ ms})$, Lat_{Nb}, and $Lat_{Nb}Amp_{NaPaNb}$.

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