Monitoring Depth of Anesthesia Utilizing a Combination of Electroencephalographic and Standard Measures

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ABSTRACT

Background: For decades, monitoring depth of anesthesia was mainly based on unspecific effects of anesthetics, for example, blood pressure, heart rate, or drug concentrations. Today, electroencephalogram-based monitors promise a more specific assessment of the brain function. To date, most approaches were focused on a "head-to-head" comparison of either electroencephalogram- or standard parameter–based monitoring. In the current study, a multimodal indicator based on a combination of both electroencephalographic and standard anesthesia monitoring parameters is defined for quantification of "anesthesia depth."

Methods: Two hundred sixty-three adult patients from six European centers undergoing surgery with general anesthesia were assigned to 1 of 10 anesthetic combinations according to standards of the enrolling hospital. The anesthesia multimodal index of consciousness was developed using a data-driven approach, which maps standard monitoring and electroencephalographic parameters into an output indicator that separates different levels of anesthesia from awake to electroencephalographic burst suppression. Obtained results were compared with either a combination of standard monitoring parameters or the electroencephalogram-based bispectral index.

Results: The anesthesia multimodal index of consciousness showed prediction probability (P_K) of 0.96 (95% CI, 0.95 to 0.97) to separate different levels of anesthesia (wakefulness to burst suppression), whereas the bispectral index had significantly lower P_K of 0.80 (0.76 to 0.81) at corrected threshold *P* value of less than 0.05. At the transition between consciousness and unconsciousness, anesthesia multimodal index of consciousness yielded a P_K of 0.88 (0.85 to 0.91).

Conclusion: A multimodal integration of both standard monitoring and electroencephalographic parameters may more precisely reflect the level of anesthesia compared with monitoring based on one of these aspects alone. **(ANESTHESIOLOGY 2014; 120:819-28)**

FOR decades, adequacy of general anesthesia was estimated on the basis of drug concentrations and unspecific clinical parameters, that is, blood pressure, heart rate (HR), patient reactions, sweating, tearing, and many more. Although these physiological responses are affected by anesthesia, they may not reflect anesthetic effects on the main target organ of anesthesia, the brain. Today, an increasing number of monitors allow a more specific assessment of effects of general anesthesia on the brain. For this purpose, these monitors record and process spontaneous electrical activity of the brain (electroencephalogram) or auditory evoked potentials. On the basis of—mostly proprietary—algorithms, these devices calculate an index value. Usually

What We Already Know about This Topic

- Indices derived from the electroencephalogram may be useful but are not optimal for assessment of depth of anesthesia
- It is unclear if an integration of measures derived from both standard and electroencephalogram monitoring may improve assessment of the hypnotic component of general anesthesia

What This Article Tells Us That Is New

- In a prospective study with 263 adult patients from six European centers undergoing surgery under general anesthesia, it was found that an index based on multimodal integration of electroencephalographic and standard monitoring parameters may more precisely assess depth of anesthesia than either standard monitoring or bispectral index monitoring alone

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this index value is a number between 0 and 100, which is inversely correlated to the hypnotic component of anesthesia or "depth" of anesthesia. These monitors provide insight into brain effects of general anesthesia, but also have limitations as they may not always adequately reflect the clinical status of a patient. Several studies showed that they may not reliably distinguish between responsive and unconscious patients.[1–6] Despite of these limitations, data suggest that use of these monitors may improve clinical outcome. The Australian B-Aware trial showed that anesthetic administration guided by bispectral index (BIS) reduces the incidence of intraoperative awareness with recall in a high-risk population.[7] These findings were challenged by the B-Unaware and the BAG-Recall trials. Both studies suggested that the incidence of awareness with recall is not reduced by a BIS-guided protocol when compared with a standard protocol based on a minimum end-tidal anesthetic gas concentration.[8,9]

These studies compared an electroencephalogram-based index with standard monitoring parameters, that is, *either* unspecific anesthesia monitoring *or* specific (brain) monitoring only. From a clinical point of view, electroencephalogram-based monitoring should not *compete with*, but *complete*, current standard monitoring.

Therefore, the current study was designed to analyze whether a multimodal integration of standard and electroencephalographic monitoring may provide reliable information about the level of anesthesia. For this purpose, an indicator was combined from electroencephalographic and standard monitoring parameters (anesthesia multimodal index of consciousness [AMIC]). It was tested whether this indicator separates consciousness from unconsciousness at the transition of both states and indicates different levels of anesthesia from wakefulness to deep anesthesia. In addition, AMIC was compared with a model from standard parameters only and with the electroencephalogram-based BIS.

Materials and Methods

Study Overview

In a European multicenter study, electroencephalogram and a variety of standard parameters were recorded synchronously during clinical anesthesia. The AMIC was designed using a combination of standard and electroencephalographic parameters. The ability of AMIC to quantify the hypnotic component of anesthesia was assessed. AMIC was compared with an index calculated from standard monitoring parameters only. In addition, stored electroencephalographic data were replayed to the BIS® (BIS A2000; Aspect Medical Systems, Norwood, MA) monitor to calculate the BIS index, and this electroencephalogram-based approach was also analyzed.

Selection of Patients

In a total of six European centers, 263 adult patients undergoing elective surgery with general anesthesia were included. Patients were recruited from August 2004 to July 2005. There was no randomization procedure, and at the time the study was performed, no formal registration was required. Still, the study was registered later at clinicaltrials.gov. After obtaining approval from the ethics committees, patients with American Society of Anesthesiologists physical status I to III gave informed written consent. Patients with contraindications to the study drugs, a history of psychiatric or neurologic diseases, drug abuse or medication known to affect the central nervous system, pregnancy, or indication for rapid-sequence induction were excluded from the study.

Study Design and Clinical Protocol

According to the hospital standards, patients were assigned to receive 1 of 10 different anesthetic regimens, combining opioids (fentanyl, remifentanil, and sufentanil), hypnotic drugs for induction (etomidate, propofol, and thiopental), and maintenance (propofol, desflurane, isoflurane, and sevoflurane), as presented in table 1. After enrollment, one patient in group 9 (induction: etomidate; maintenance: propofol–sevoflurane) did not receive propofol, but only etomidate and sevoflurane. As per intention to treat, he was included in group 9. Each patient obtained a specific combination of opioids and hypnotic drugs according to the standard clinical practice in the according hospital. Each study center used at least two anesthetic regimens and each anesthetic regimen was used in at least two different study centers. All anesthetic and surgical interventions were recorded in a standardized manner. During induction, patients were asked every 15 s to squeeze the investigator's hand. A response was verified by an immediate repetition to differentiate involuntary movement from a response to command. Loss of consciousness (LOC) was defined as a missing response to a repeated verbal command. When neuromuscular-blocking agents were given, Tunstall's[10] isolated forearm technique was used to preserve the patient's ability to follow command. For this purpose, a tourniquet was inflated on the right forearm before a

Table 1. Anesthetic Combinations for Induction and Maintenance

Group	Drug (Induction/Maintenance)	No. Patients
1	Thiopental-opioid/isoflurane-opioid	40
2	Etomidate-opioid/isoflurane-opioid	35
3	Propofol–remifentanil/propofol–remifentanil	37
4	Propofol-sufentanil/propofol-sufentanil	20
5	Propofol-opioid/desflurane-opioid	40
6	Propofol-opioid/sevoflurane-opioid	21
7	Propofol-opioid/isoflurane-opioid	30
8	Etomidate-sufentanil/propofol-sufentanil	14
9	Etomidate-sufentanil/propofol-sevoflurane-sufentanil	20
10	Etomidate-sufentanil/propofol-isoflurane-sufentanil	6

In six different groups, general anesthesia was induced with an intravenous anesthetic (middle column, left) and maintained either with an intravenous or a volatile anesthetic (middle column, right). If the opioid is not specified, different opioids were used.

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muscle relaxant was injected into a vein either proximal to the tourniquet or on the opposite arm. Intact neuromuscular transmission was not verified to avoid additional painful stimuli. After skin incision, anesthetic concentrations were increased until the electroencephalogram showed burst suppression (BS) with a minimum of 1 s suppression in the electroencephalogram ("silent second"). Subsequently, drug concentrations were decreased and general anesthesia was maintained according to standard clinical practice until end of surgery. At the end of surgery, drug administration was stopped and patients were asked to squeeze the investigator's hand again. The first verified squeeze of hand marked return of consciousness (ROC). Study design and selected data points used in the analysis are shown in figure 1. Once recovered from anesthesia, patients were assessed for awareness with recall using a structured interview.[11] This interview was repeated within 3 days on the ward.

Monitoring and Data Recording

Anesthesia standard monitoring parameters (noninvasive blood pressure, HR, oxygen saturation, end-tidal carbon dioxide concentration, anesthetic gas concentrations, and respiratory variables; table 2) were continuously measured with a VisiCon M211 patient monitor (BBraun, Melsungen, Germany) and stored together with relevant patient data (*e.g.*, age, weight, and American Society of Anesthesiologists status) on disk. In addition, two electroencephalographic channels were recorded continuously and stored using an amplifier developed for intraoperative electroencephalographic recordings (total bandwidth 0.5 to 400 Hz using analog filters, sampling rate 1,000 Hz, 12-bit amplitude resolution). This device had been developed for a European multicenter study.[12,13] It is based on a digital signal processing board in a personal computer and an isolated preamplifier unit. The preamplifier is powered by two AA-cells and has integrated auditory and somatosensory stimulators, automatic calibration, and impedance checking. A detailed description of the equipment has been published before.[14,15] Four self-adhesive electroencephalographic/electrocardiographic electrodes (BlueSensor N; Ambu A/S, Ballerup, Denmark) were positioned at AT1, M2, Fz (reference), and Fpz (ground) according to the international 10 to 20 system. At each electrode position, the skin was degreased with alcohol to maintain electrode impedances below 5 kΩ. Automated artifact rejection was used to discard signal segments of 10 s length with amplitudes greater than 250 μV, slopes greater than 140 μV/ms, or zero-signals of defined minimal length.[16] The electroencephalogram was preprocessed using a digital low-pass filter at 30 Hz (subsequent downsampling at 200 Hz) to improve signal to noise ratio and to reduce the influence of high-frequency content (with potential electromyogram influence) on the electroencephalogram. Electroencephalographic parameters were calculated from signal segments of 10 s length with a 5 s overlap. In addition, recorded electroencephalogram was replayed using a play-back device[17] for off-line evaluation of the BIS.

Selection of AMIC Variables

The AMIC design integrates variables derived from the electroencephalogram, standard monitoring parameters, individual patient data, and drug information (table 2). Electroencephalographic parameters for the AMIC model were selected on the basis of previous studies.[5,16,18–20] They consist of the weighted spectral median frequency (particularly designed to separate consciousness and unconsciousness at the transition between both states),[20] the approximate entropy (ApEn; nonlinear electroencephalographic characteristics, monotonic behavior during deepening of anesthesia),[18,19] permutation entropy (PeEn; nonlinear electroencephalographic characteristics, robust against artifacts, nonlinear signal characteristics, reliably separates consciousness and unconsciousness),[16] and suppression ratio (SuppRatio; amplitude based detection of detection of BS patterns).[19,21] Selection of standard monitoring parameters and patient and drug information was based on clinical expert's opinion. HR and mean arterial blood pressure (MAP) were selected to provide information about cardiovascular status. The additional parameters HR trend (ΔHR) and BP MP trend (ΔMAP) were calculated as the difference between two subsequent measurements. Respiratory parameters were the calculated difference between in- and expiratory

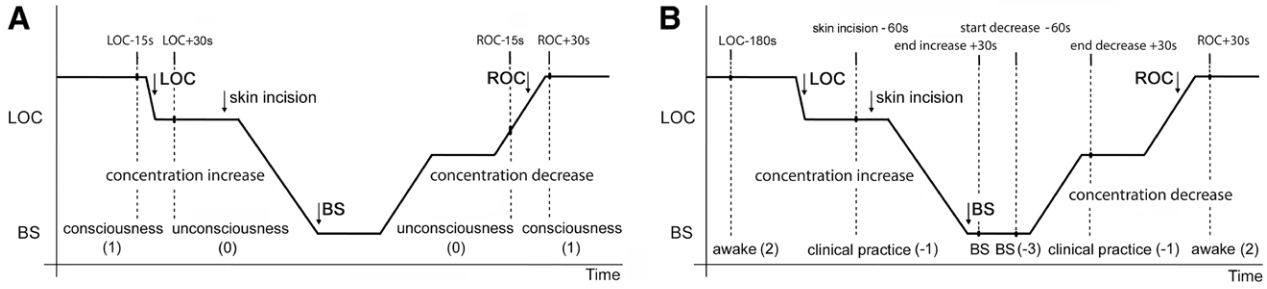

Fig. 1. Study diagram showing time points loss of consciousness (LOC), skin incision, burst suppression (BS), and return of consciousness (ROC) and phases of concentration increase and decrease. We performed data analysis at selected time points reflecting (*A*) the transition between *consciousness* (phase 1, time points LOC −15 s and ROC + 30 s) and *unconsciousness* (phase 0, LOC + 30 s and ROC −15 s,) and (*B*) levels *awake* (phase 2, LOC −180 s, ROC + 30 s), *anesthesia according to clinical practice* (phase −1, skin incision −60 s, end decrease +30 s) and *BS* (phase −3, end increase +30 s, start decrease −60 s).

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Table 2. Overview of the Parameters Used in the Anesthesia Multimodal Index of Consciousness Divided in Electroencephalographic Parameters, Parameters of Standard Monitoring, Drug Protocol, and Individual Patient Data

Source	Parameter Name	Abbreviation	Sampling Rate	Short Description
Electroencephalogram	Weighted spectral median frequency	WSMF	10 s	Spectral analysis parameter, frequency range 8–30 Hz; detection of consciousness and unconsciousness at state transition
	Approximate entropy	ApEn	10 s	Entropy, statistical measure of regularity, frequency range 0.5–30 Hz; separation of different anesthetic levels
	Permutation entropy	PeEn	10 s	Entropy, statistical measure of regularity, frequency range 0.5–30 Hz; detection of consciousness and unconsciousness at state transition
	Suppression ratio	SuppRatio	30 s	Ratio of suppression to nonsuppression periods; detection of burst suppression pattern
Standard monitoring	Heart rate	HR	1 min	
	Mean arterial blood pressure	MAP	5 min	
	Difference between in- and expiratory oxygen concentration	Gas O_2 IE	1 min	Measured during mechanical ventilation, calculated as difference between inspiratory and expiratory oxygen concentration
	End-expiratory carbon dioxide concentration	Gas CO_2 exp	1 min	Measured during mechanical ventilation
	Peak inspiratory pressure	SPIRO Ppeak	5 min	Measured during mechanical ventilation
	Heart rate trend	ΔHR	1 min	Rate of change of the HR, reflects trend information
	Mean arterial blood pressure trend	ΔMAP	5 min	Rate of change of the MAP, reflects trend information
Drug	MAC equivalent of difference between in- and end-expiratory gas concentration	MAC IE	1 min	Measured during mechanical ventilation, calculated as difference of MAC values between inspiratory and end-expiratory concentration
	MAC equivalent of end-expiratory gas concentration	MAC exp	1 min	Measured during mechanical ventilation
	Plasma concentration	Cp	10 s	Calculated during propofol infusion according to Marsh model
	Induction drug	Drug Ind	Constant	Anesthetic agent used in the induction phase of anesthesia
	Maintenance drug	Drug Main	Constant	Anesthetic agent used in the maintenance phase of anesthesia
Patient	Age, sex, BMI	Age, sex, BMI	Constant	Individual patient information

ApEn = electroencephalographic approximate entropy; BMI = body mass index; Cp = plasma concentration; Drug Ind = induction drug; Drug Main = maintenance drug; Gas CO_2 exp = end-expiratory carbon dioxide concentration; Gas O_2 IE = difference between in- and expiratory oxygen concentration; HR = heart rate; MAC = monitored anesthesia care; MAC exp = MAC equivalent of end-expiratory gas concentration; MAC IE = MAC equivalent of difference between in- and end-expiratory gas concentration; MAP = mean arterial blood pressure; PeEn = electroencephalographic permutation entropy; SPIRO Ppeak = peak inspiratory pressure; SuppRatio = electroencephalographic suppression ratio; WSMF = electroencephalographic weighted spectral median frequency; ΔHR = heart rate trend; ΔMAP = mean arterial blood pressure trend.

oxygen concentration (Gas O_2 IE), end-expiratory carbon dioxide concentration (Gas CO_2 exp), peak inspiratory pressure (SPIRO Ppeak), end-expiratory gas concentration (monitored anesthesia care [MAC] exp; MAC values calculated according to Nickalls *et al.*[22]), differences between inspiratory and end-expiratory volatile anesthetic concentration (MAC IE; MAC values calculated according to Nickalls *et al.*[22]), which may contain information about the current dynamics of the anesthetic level (*i.e.*, increase or decrease of the volatile concentration), propofol plasma concentrations according to the Marsh[23] model (Cp), induction and maintenance drug (Drug Ind/Main), age, sex, and body mass index. Parameters were recorded with respect to specific sampling rates, for example, 10 s for electroencephalographic parameters, 5 min for blood pressure, and time-constant demographic patient data (table 2). Trend values ΔHR and ΔMAP are indicated by the time derivative over two consecutive measurements. Finally, different time scales were resampled using a sliding window technique to provide synchronous parameter updates every 5 s.

Design of the AMIC

An Adaptive Neuro Fuzzy Inference System[24–26] was used to generate the AMIC. Standard monitoring parameters were preselected on the basis of clinical expert knowledge and electroencephalographic parameters according to preliminary analysis (table 2). Knowledge based on the current data was not used for parameter preselection for design of the AMIC model. In a stepwise approach, the model was designed to

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reach: A. "*distinction between consciousness and unconsciousness at the transition between these conditions*" and B. "*recognition of wakefulness, anesthesia according to clinical practice, and excessively deep anesthesia (*electroencephalographic *BS)*." Subsequently, the AMIC model was developed, integrating indicators for A. and B. into an index. Figure 2 shows the workflow for real-time AMIC processing from data acquisition to the two-step classification procedure.

During the procedure of model generation, specific rules are constructed for incomplete input parameter values. Therefore, the Adaptive Neuro Fuzzy Inference System model allows the generation of valid AMIC values even if single subparameters are missing. For model generation (training and test) of the AMIC study, data were retrospectively analyzed (see Statistical Analysis).

Because it has been questioned whether addition of electroencephalographic parameters may improve standard clinical monitoring,[27] it was analyzed whether a combination of standard monitoring may reach similar results. Therefore, a data-driven model was designed which only includes standard parameters. For this purpose, a basis parameter set including HR, MAP, Cp, and MAC exp was supplemented by all permutations of remaining standard parameters, drug and patient information. The data-driven model leading to best prediction performance was identified and used for comparison.

Statistical Analysis

The aim of the current study was to evaluate the ability of AMIC to separate different anesthesia states. In addition, the performance of the indicator including standard monitoring parameters (reflecting only indirect anesthetic brain effects) and of BIS (only electroencephalographic parameters) was evaluated for the same clinical questions. Therefore, indicators were calculated from data pairs before and after LOC (time points LOC −15 s, LOC +30 s) and ROC (time points ROC −15 s, ROC +30 s) to analyze their ability to separate *consciousness* from *unconsciousness* at the transition between these states (fig. 1A). The interval of 15 s in asking the patient to squeeze hand allows a clear definition of the clinical endpoints LOC/ROC, and thus allows the conclusion that 15 s before ROC (LOC) the patient was unconscious (conscious). To compensate for time delays of the electroencephalographic monitor,[4] a computing time of 30 s after LOC/ROC was added. Second, differentiation of levels *awake* (LOC −180 s, ROC +30 s), *anesthesia according to clinical practice* (skin incision −60 s, end of anesthetic decrease +30 s), and *BS* (end of anesthetic increase +30 s, start anesthetic decrease −60 s) was performed for indicator assessment (according to fig. 1B).

Prediction probability (P_K) was used to assess performance of the indicators.[28,29] P_K is a dimensionless number between 0 and 1, where 1 reflects a perfect separation of

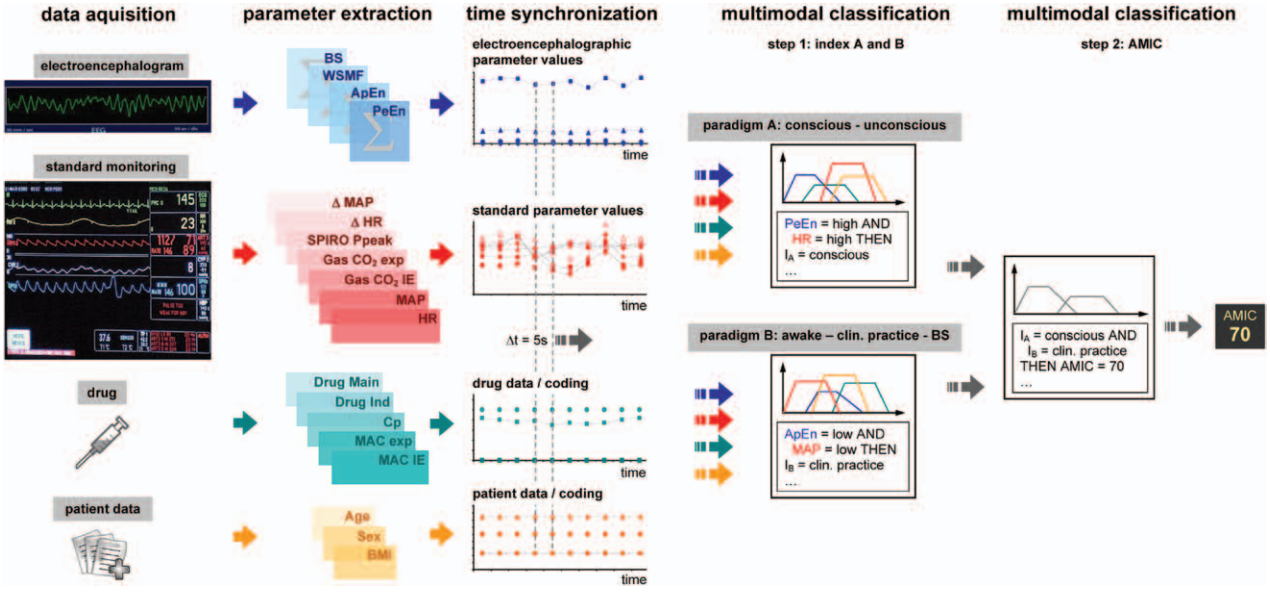

Fig. 2. Workflow for (real-time) computation of the anesthesia multimodal index of consciousness (AMIC). After data acquisition (including preprocessing, *e.g.*, artifact detection), parameters (according to table 2) are extracted for each modality. Independent of the sampling rate of specific parameters (*e.g.*, 10 s for electroencephalographic parameters and constant in case of patient age), each parameter is resampled at 5 s and synchronized in time to obtain a multivariate time series. In a first step, classification is performed in two independent models (model A trained for separation of consciousness and unconsciousness and model B trained for separation of different hypnotic states from wakefulness to burst suppression) using an Adaptive Neuro Fuzzy Inference System. Both models were trained to provide best fit of input data to paradigm A and B, leading to data reduction for further processing. In a second step, resulting indices A and B are combined by a third Adaptive Neuro Fuzzy Inference System model resulting in AMIC. ApEn = approximate entropy; BMI = body mass index; BS = burst suppression; HR = heart rate; MAC IE = monitored anesthesia care equivalent of difference between in- and end-expiratory gas concentration; MAP = mean arterial blood pressure; PeEn = permutation entropy; WSMF = weighted spectral median frequency.

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Table 3. Number of Patients and Percentage of Included Anesthetic Regimen in Each Cross-validation Group

Drug Group	Cross-validation Group No. Subjects	I 90	II 88	III 85
1	Anesthetic regimen in indicated groups (%)	15.6	15.9	14.1
2		14.4	11.4	14.1
3		13.3	14.8	14.1
4		6.7	8	8.2
5		15.6	15.9	14.1
6		8.9	6.8	8.2
7		10	12.5	11.8
8		5.6	4.5	5.9
9		7.8	8	7.1
10		2.2	2.3	2.4

different clinical states, 0.5 reflects a random result, and 0 reflects a 100% disagreement between monitor and clinical status. Estimation of uncertainty was based on 95% percentile bootstrap CIs.[28,30] P_K was calculated at predefined time points as described above.

A three-fold cross-validation was performed for the AMIC model generation to avoid overfitting through overlapping training and test data: A number of patients as equal as possible was randomly assigned to each of the three groups (I: 90 patients, II: 88, III: 85) by keeping all anesthetic combinations in the three groups to provide training and test of the AMIC on different patients but based on analogous anesthetic procedures. The AMIC was consecutively trained on data of two groups (I + II, I + III, II + III) to identify three models leading to maximum overall P_K (awake/consciousness, unconsciousness, clinical practice, BS). These models were evaluated on data of the remaining third group (III, II, I) to provide AMIC values in data of all 263 patients for final model evaluation.

Comparison of AMIC, standard parameter indicator, and of BIS was performed using percentile bootstrap CIs of P_K ($P < 0.05$, Bonferroni correction for multiple comparisons).[28] Patient characteristics and demographic data in both groups were calculated and compared with *t* tests and chi-square test (two-sided tests with unequal variances).

Results

Data of 263 study patients were included in the analysis, 111 were men (42%) and 152 women (58%). Age (mean ± SD) was 50.1 ± 13.7 yr, height was 172 ± 9 cm, and weight was 77 ± 16 kg. American Society of Anesthesiologists physical status was I in 101 patients, II in 115 patients, and III in 47 patients. Demographic data did not show significant differences between groups with different anesthetic regimens (table 1). No patient reported awareness with recall.

All parameters listed in table 2 were used for the AMIC. Model generation was based on a three-fold cross-validation according to the data of groups I, II, and III in table 3. The table indicates the number of patients and the percentage of anesthetic regimens included in each group. The model of an indicator which was based on standard monitoring parameters leading to a highest overall P_K (awake/consciousness, unconsciousness, clinical practice/BS) included the following clinical parameters: HR, MAP, Cp, MAC exp, Gas carbon dioxide exp, SPIRO Ppeak, and ΔMAP (table 2). On the basis of standard monitoring parameters, a P_K of 0.81 (0.77 to 0.84) was obtained during the transition between consciousness and unconsciousness, which is significantly lower than a P_K of 0.88 (0.85 to 0.91) as obtained for the AMIC (all anesthetic combinations, $P < 0.05$ corrected). In contrast, separation of levels awake and clinical practice yields to equal P_K of 1.00 for AMIC and for the indicator of standard monitoring parameters.

Results of the AMIC and BIS are shown in table 4. A comparison of AMIC with BIS shows a better discrimination of clinical states for the new indicator. Figure 3 illustrates the distribution of indicator values of AMIC (fig. 3A) and BIS (fig. 3B) for selected anesthetic levels and all anesthetic combinations. In AMIC model generation, BS was used as an electroencephalographic endpoint representing deep anesthesia. The AMIC provides a similar P_K for

Table 4. P_K Statistics of the AMIC and of the BIS with Respect to Different Anesthetic Combinations and to Different Levels Formed from the Anesthesia States Contained in the Data sets A, B, and A and B

Data (Anesthetic Levels)	No. of Data Points	P_K AMIC	P_K BIS	Comparison
A Conscious-unconscious	479-526	0.88 (0.85–0.91)	0.74 (0.70–0.78)	0.09–0.20*
B Awake-clinical practice-BS	479-336-335	0.97 (0.95–0.97)	0.76 (0.70–0.76)	0.19–0.27*
B Awake-clinical practice	479-336	1.0 (1.00–1.00)	0.86 (0.82–0.90)	0.09–0.19*
A and B Awake/consciousness-unconsciousness-clinical practice-BS	742-526-336-335	0.96 (0.95–0.97)	0.80 (0.76–0.81)	0.15–0.20*

95% percentile bootstrap CIs of prediction probability (P_K) excluding 0.5 indicate whether the indicators separate the levels significantly better than chance. Intervals for pair-wise comparison of AMIC and BIS indicate significant differences of P_K for both indicators (all anesthetic combinations) if zero is excluded from the range.

*$P < 0.05$ corrected.

AMIC = anesthesia multimodal index of consciousness; BIS = bispectral index; BS = electroencephalographic burst suppression; *P* = level of significance; P_K = prediction probability.

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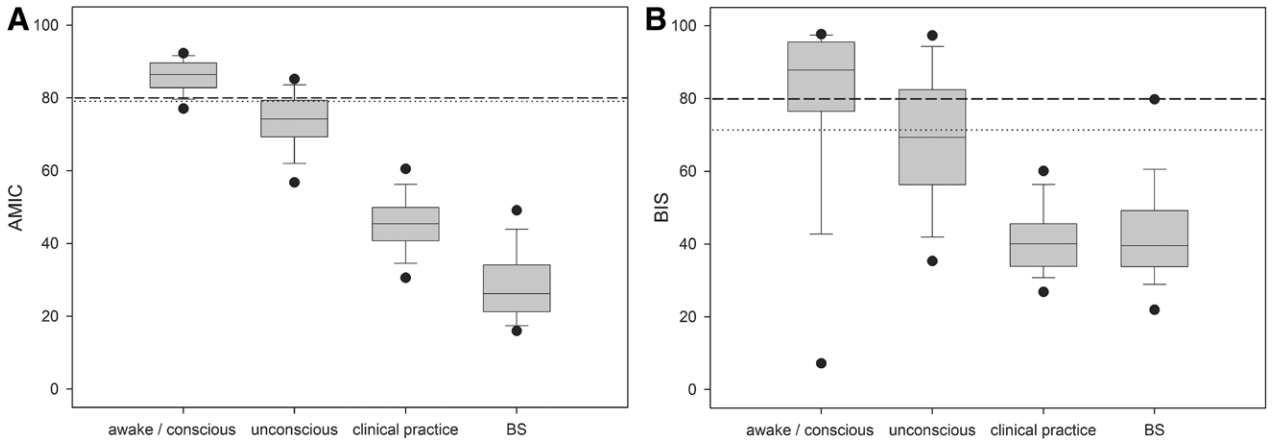

Fig. 3. Indicator value distribution of the anesthesia multimodal index of consciousness (AMIC; *A*) and bispectral index (BIS; *B*) for the different anesthetic levels (*central line*: median, *dots*: 5% and 95% percentiles, *whiskers*: 10% and 90% percentiles, *boxes*: 50% quartile). Analyzed data consist of 742 data points for awake and consciousness, 526 data points for unconsciousness, 336 data points for anesthesia according to clinical practice, and 335 data points for burst suppression (BS). *Horizontal dashed lines* indicate optimum threshold (based on maximum sum of sensitivity and specificity) for separation of consciousness *versus* unconsciousness (AMIC: 80, BIS: 80) and for separation of awake/consciousness *versus* unconsciousness/clinical practice/BS (AMIC: 79, BIS 72).

separation of levels awake/consciousness, unconsciousness, clinical practice without inclusion of data from the level BS (0.95; 0.94 to 0.98) compared with the P_K from data including BS (0.96; 0.95 to 0.97).

In these analyses, AMIC was reconstructed in all data of the 263 patients based on three independent models obtained from the cross-validation. The individual models which were trained on data of two groups (I + II, I + III, II + III) and tested on data of the groups III, II, I lead to overall P_K ranging between 0.94 and 0.96, which is comparable with the P_K of 0.96 of the model used in evaluation of all 263 patients (separation of all levels).

Discussion

The current study shows that a combination of standard monitoring and electroencephalographic parameters can distinguish different levels of anesthesia better than either standard monitoring or electroencephalogram-based BIS monitoring alone.

For this purpose, the AMIC was developed and evaluated (three-fold cross-validation) on the basis of data of a European multicenter study. The AMIC combines "state-of-the-art" electroencephalographic parameters, standard monitoring, drug and patient information. This approach was chosen to combine the additional information from the electroencephalogram with standard monitoring practice rather than to perform a "head-to-head" comparison between two approaches. In our point of view, this reflects a clinical approach to electroencephalogram-based monitoring of anesthesia. Compared with standard (nonelectroencephalographic) monitoring, information about anesthetic effects on the main target organ of anesthesia, the brain, is added. It seems unlikely that this additional information can replace (unspecific) standard monitoring. Therefore, we chose a monitoring approach which reflects the aspect that information about cortical effects is added. This point of view is supported by the results at the transition between consciousness and unconsciousness, where P_K = 0.88 of the AMIC (electroencephalographic and standard monitoring parameters) is significantly higher than the P_K = 0.81 of the standard parameter model alone.

The study was designed to test whether the combined indicator reliably separates consciousness from unconsciousness and indicates increase and decrease of the anesthetic level over the entire range from light sedation to deep anesthesia.

As a challenging approach, the transition from consciousness to unconsciousness and *vice versa* was used to assess the anesthesia indices. (Un)consciousness was defined as (un) responsiveness to command. This approach may have limitations, for example, it requires an active response of the patient.[31] Still, it provides one of the few clinical endpoints with a marked change in patient status. In clinical anesthesia, LOC represents only one endpoint of the entire range of general anesthesia. "Deeper" anesthesia can be achieved with increasing drug concentrations. This "deepening" of the level of anesthesia may not only be reflected by cortical effects.[32] As a consequence, AMIC includes both electroencephalographic and nonelectroencephalographic parameters.

On the basis of the data of the current study, the AMIC outperforms both the "electroencephalographic-only" BIS and the standard monitoring parameters approach. Several paradigms were used to assess the AMIC, with a focus on the dynamic transition between consciousness and unconsciousness at LOC and ROC.

The patient individual model design used here includes data from different sources: target electroencephalogram with high temporal resolution, nonspecific standard

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monitoring data which provide additional trend information with lower time resolution, and individual patient data and drug protocols. The indicator AMIC integrates these modalities by sophisticated multiscale data-driven fuzzy inference including "state-of-the-art" parameters for quantifying anesthetic-induced effects in the electroencephalogram. The proposed AMIC approach additionally stabilizes the integration of multimodal and multiscalar data through the "bridging" of missing values that may occur during clinical anesthesia, for example, as a result of artifacts or delayed data acquisition. This is reached by a flexible adaptation of the model's built-in set of rules, weighting each integrated parameter individually. Thus, an AMIC value is calculated even if the number of input variables is incomplete.

Results show significant advantages of this multimodal approach. In particular, at the transition between consciousness and unconsciousness, the AMIC provides P_K of 0.88, which is significantly higher than P_K of 0.74 for BIS (corrected threshold $P < 0.05$). In the detection of anesthetic-induced transitions from wakefulness to BS (including onset, respectively fading of unconsciousness and changes in anesthetic levels according to clinical practice), we found a P_K of 0.96 for the AMIC, which is significantly higher than P_K of BIS (0.80) at corrected thresholds P value of less than 0.05. This indicates that electroencephalographic information alone only reflects one aspect of the clinical status of the patient. However, in a calculation scheme without electroencephalographic information, that is, a combination from standard monitoring parameters, the indicator reaches a lower P_K value than the AMIC (incorporating both, electroencephalographic and physiologic measures). In concordance with previous findings, this shows that monitoring on the basis of standard clinical practice may also result in an incomplete picture. Our findings are supported by results of the BAG-Recall trial, where the electroencephalogram-based parameter BIS does not outperform an approach based on a standard monitoring parameter.

The AMIC fundamentally differs from existing electroencephalographic monitors of the hypnotic component. It can be considered as an expert system that delivers probabilistic decision support regarding depth of anesthesia. Accurate detection of consciousness and unconsciousness at the transition between both states indicates that the multimodal indicator benefits from analysis methods allowing short periods of 10 s for adequate electroencephalographic signal processing: On the basis of previous studies, a generalized spectral parameter (weighted spectral median frequency) has been developed to provide reliable separation of consciousness and unconsciousness at the transition between both states.[20] Additional information that may be related to the dynamics of the cerebral cortex is reflected by nonlinear electroencephalographic characteristics. Therefore, the nonlinear parameter entropy seems to be an appropriate approach to quantify the hypnotic component of anesthesia, because LOC is related to a change in information processing in neuronal networks.[33,34] The AMIC includes the ordinal approach of PeEn quantifying characteristics of the electroencephalogram related to the information content of the signal.[16,35] It allows reliable estimates using electroencephalographic signals of a few seconds length ensuring very short time delays for indicator calculation.

If frequencies of the electroencephalographic γ-band are included in index calculation, detection of consciousness may also be affected by frontal muscle activity. In particular with frontal electrodes, there is an overlap in frequency ranges of electroencephalogram and electromyogram, with usually higher amplitudes of frontal electromyographic activity.[21,36] The AMIC algorithm is independent from the electroencephalographic γ-band, which improves signal to noise ratio of target electroencephalographic analysis,[37] that is, it reduces the influence of overlapping frontal muscle electromyogram to frontal electroencephalogram. Methods of PeEn, ApEn, and weighted spectral median frequency have been integrated into the model. In previous studies, PeEn and weighted spectral median frequency provided significantly higher discrimination power in separating consciousness from unconsciousness at the transition between both states compared with the discrimination power provided by BIS, even if only electroencephalographic frequencies up to 30 Hz are included in the calculation.[16,20] In contrast, ApEn reflects changes in low-dimensional dynamical processes, which can be used for reliable indication of the hypnotic state from light to deep anesthesia with electroencephalographic BS.[19]

There are some potential limitations of the current study: Even if the evaluation of the AMIC was based on a cross-validation, the comparison of AMIC and BIS may be biased in favor of the AMIC, because data from the same clinical study were used for the AMIC model generation, but of course unknown to BIS. Nevertheless, results suggest that overfitting to the data represents a minor effect, as we obtained similar P_K of 0.94 to 0.96 for AMIC evaluation based on the three separate test data sets and a P_K of 0.96 for evaluation performed on the whole data (separation of levels awake/consciousness, unconsciousness, clinical practice, BS). An unbiased analysis of AMIC and other traditionally used monitoring paradigms should be based on independent data from a prospective evaluation study.

AMIC was designed to separate unconsciousness from wakefulness, and to reflect the entire range from awake to deep anesthesia. For this purpose, "deep anesthesia" was defined as electroencephalographic BS with a minimum of 1 s suppression in the electroencephalogram ("silent second"). This may induce a bias toward electroencephalogram in the selection of parameters. This potential limitation of this approach was accepted, because it allows a definition of "deep anesthesia" based on effects in the main target organ of anesthesia, the brain, whereas other clinically used parameters, for example, bradycardia, hypotension, would

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focus on side effects rather than the main effect of anesthetics. P_K obtained from data with BS (P_K = 0.96) or without BS (P_K = 0.95) were similar, indicating that inclusion of BS in the model generation does not strongly bias the behavior of the AMIC.

In the current study, there were no data from patients awake during neuromuscular blockade. Therefore, it remains unclear whether such a patient would be detected by AMIC. The main effect of neuromuscular blockade is a reduction of muscle activity in the electroencephalographic signal. Muscle activity is mainly prominent in the range of high frequencies. Therefore, a selection of electroencephalographic parameters which are not based on high-frequency components of the signal for the AMIC suggests that detection of awake patients should also be reached under neuromuscular blockade.

Furthermore, unevenly distributed sample sizes and different surgical procedures for included anesthetic combinations may bias results if the drug protocol has an influence on indicator values. Therefore, additional studies are required to validate results of the current study.

In summary, AMIC combines traditional parameters used to assess the hypnotic component of anesthesia with a measurement from the main target organ, the brain. This combination allows a better separation of different anesthetic levels than standard monitoring parameters or electroencephalographic monitors alone.

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Competing Interests

E. F. Kochs, G. Schneider, D. Jordan, A. Omerovic, and M. Kreuzer have applied for a European (11178111.8; filing date: August 19, 2011, priority date: June 17, 2011) and international (PCT/EP2012/002 158; filing date: May 21, 2012) patent. All other authors declare no competing interests.

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Appendix

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