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Time Delay of Index Calculation

Analysis of Cerebral State, Bispectral, and Narcotrend Indices

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Background: **On the basis of electroencephalographic analysis, several parameters have been proposed as a measure of the hypnotic component of anesthesia. All currently available indices have different time lags to react to a change in the level of anesthesia. The aim of this study was to determine the latency of three frequently used indices: the Cerebral State Index (Danmeter, Odense, Denmark), the Bispectral Index (Aspect Medical Systems Inc., Newton, MA), and the Narcotrend Index (MonitorTechnik, Bad Bramstedt, Germany).**

Methods: **Artificially generated signals were used to produce up to 14 constant index values per monitor that indicate "awake state," "general anesthesia," and "deep anesthesia" and smaller steps in between. The authors simulated loss of and return to consciousness by changing between the artificial electroencephalographic signals in a full-step and two stepwise approaches and measured the time necessary to adapt the indices to the particular input signal.**

Results: **Time delays between 14 and 155 s were found for all indices. These delays were not constant. Results were different for decreasing and increasing values and between the full-step and the stepwise approaches. Calculation time depended on the particular starting and target index value.**

Conclusions: **The time delays of the tested indices may limit their value in prevention of recall of intraoperative events. Furthermore, different latencies for decreasing and increasing values may indicate a limitation of these monitors for pharmacodynamic studies.**

MONITORING of the hypnotic component of anesthesia using electroencephalogram-derived indices has become increasingly popular during the past decade. Several different indices are available. The Bispectral Index (BIS; Aspect Medical Systems Inc., Newton, MA) is an empirically derived multifactorial electroencephalographic parameter.[1] It is a dimensionless number between 0 and 100. In nonanesthetized patients, the BIS ranges between 90 and 100. Total suppression of electrical activity on the cortical level results in a BIS of 0. According to the manufacturer, BIS values below 60 are associated with a low probability of consciousness.|| The Narcotrend® monitor (MonitorTechnik, Bad Bramstedt, Germany) quantifies electroencephalographic changes induced by anesthesia using a multivariate statistical algorithm. In the latest version of Narcotrend®, a numerical index is calculated in addition to the alphanumerical classification of stages. Analogous to the BIS, the Narcotrend index (NCT) is a dimensionless number between 0 and 100 that inversely correlates with depth of hypnosis.[2,3]

The Cerebral State Index (CSI; Danmeter, Odense, Denmark) has recently been introduced as a measure of the hypnotic component of anesthesia. It is calculated by the Cerebral State Monitor (CSM), a portable handheld device. Like the BIS, the CSI is a dimensionless number between 0 and 100 and was developed to monitor the level of consciousness during general anesthesia. Calculation of the CSI is based on a complex algorithm that uses four subparameters[4,5] calculated from the spontaneous electroencephalogram: β-ratio, α-ratio, β-ratio $-$ α-ratio, and burst-ratio. These parameters are defined as follows:

$$\beta\text{-ratio} = \log \{E(30 - 42.5\ \text{Hz})/E(11 - 21\ \text{Hz})\}$$

$$\alpha\text{-ratio} = \log \{E(30 - 42.5\ \text{Hz})/E(6 - 12\ \text{Hz})\}$$

$$\beta\text{-ratio} - \alpha\text{-ratio} = \log \{E(6 - 12\ \text{Hz})/E(11 - 21\ \text{Hz})\}$$

Burst-ratio is defined as the percentage of time in a 30-s window where the amplitude of the electroencephalogram is less than 3.5 μV.

These four subparameters correlate individually with the level of anesthesia, but as a single measure, their correlation coefficient is low. A more reliable assessment of depth of hypnosis may be achieved when the four subparameters are used as inputs of an adaptive neuro-fuzzy inference system.[6] Its output is the CSI. The adaptive neuro-fuzzy inference system was designed to use the best applicable subparameter or a combination to reach a higher correlation with the level of hypnosis. The adaptive neuro-fuzzy inference system is a fuzzy logic system and does not depend on a mathematical function that deduces the correlation between values

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|| Kelley SD: Monitoring Level of Consciousness during Anesthesia & Sedation: A Clinician's Guide to the Bispectral Index®. Available at: http://www.aspectmedical.com/assets/documents/pdf/complete_bis_handbook.pdf. Accessed September 19, 2005.

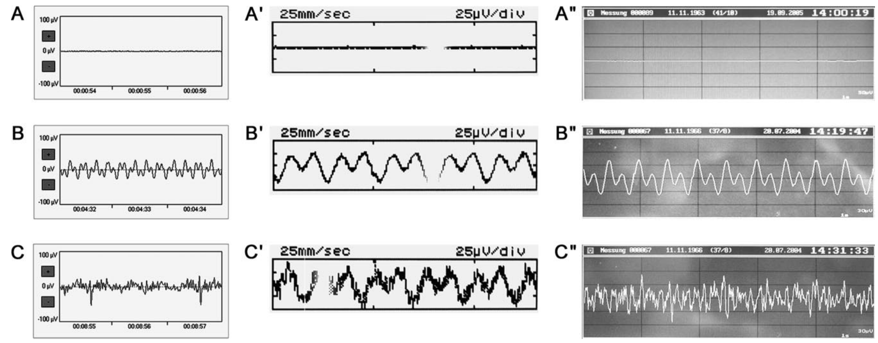

Fig. 1. Three electroencephalographic signals were artificially generated for Cerebral State Index, Bispectral Index (′), and Narcotrend Index (″): (*A*) Signal "deep anesthesia" is represented by a missing input signal and is characterized by a "flat" electroencephalogram. (*B*) Signal "awake." (*C*) Signal "general anesthesia." The characteristics of each used signal can be found in the Web Enhancement.

calculated from the electroencephalogram and the patient's clinical state. The exact algorithm of CSI calculation has not been published. Furthermore, the selection of adequate subparameters by a fuzzy logic system for the respective frequency content of the electroencephalogram has not been revealed in detail by the inventor.

All available monitors require some time to calculate an index value.[7] The exact duration of this delay is unknown for most monitors but is a major factor for the efficacy of a monitor. This may in particular be critical for detection of awareness or at transitions from awareness to unconsciousness or *vice versa*. The aim of the current study was to determine this delay for CSI, BIS, and NCT at transitions between "awake," "general anesthesia," and "deep anesthesia."

Materials and Methods

The study was designed to measure time delays of CSI, BIS, and NCT at the transition between different index levels. For this purpose, we used up to 14 artificially generated electroencephalographic signals for each monitor. All signals consisted of up to four sine waves and noise (fig. 1) and produced constant index values for more than 2 min. Additional information regarding the signals is available on the ANESTHESIOLOGY Web site, http://www.anesthesiology.org. Cortical suppression was represented by a missing input signal. The missing signal ("deep anesthesia") produced CSI and BIS values of 0 and an NCT value of 5 (CSI 0, BIS 0, NCT 5; figs. 1A–A″). Two signals were generated, representing "general anesthesia" (CSI 42, BIS 52, NCT 46; figs. 1B–B″) and "awake" (CSI 89, BIS 98, NCT 94; figs. 1C–C″). Furthermore, we compiled a series of artificial signals that simulated smaller steps in transition from one input signal to the next. These signals caused the corresponding monitors to indicate the following index values: CSI: 9, 18, 28, 44, 50, 60, 64, 79, 91, and 100; BIS: 9, 21, 38, 52, 63, 74, and 86; NCT: 14, 23, 31, 46, 61, 73, 79, and 93. Signal requirements were that (1) stable index values were produced and (2) signal quality was high (*i.e.*, the monitors did not classify the signal as artifact). The original signals can be obtained from the authors on request.

Data Analysis

Transitions between the three conditions were analyzed. We simulated increase and decrease of index values in a stepwise manner and in a full increase/decrease: First, a full step from "deep anesthesia" to "awake" and back was simulated (fig. 2). Second, an intermediate level was added, *i.e.*, a stepwise change from "deep anesthesia" to "general anesthesia," then to "awake" and back (fig. 3). Third, we performed a sequence of signal changes which produced smaller steps during increase and decrease of index values (fig. 4).

We recorded the time required by each monitor to indicate the index value of the particular input signal. CSI data were transferred to and stored on a personal computer using the wireless CSM link and CSM on-line capture device. The CSM capture device allows the recording of the time-dependent course of CSI values. Stored CSI data were used to analyze the time interval

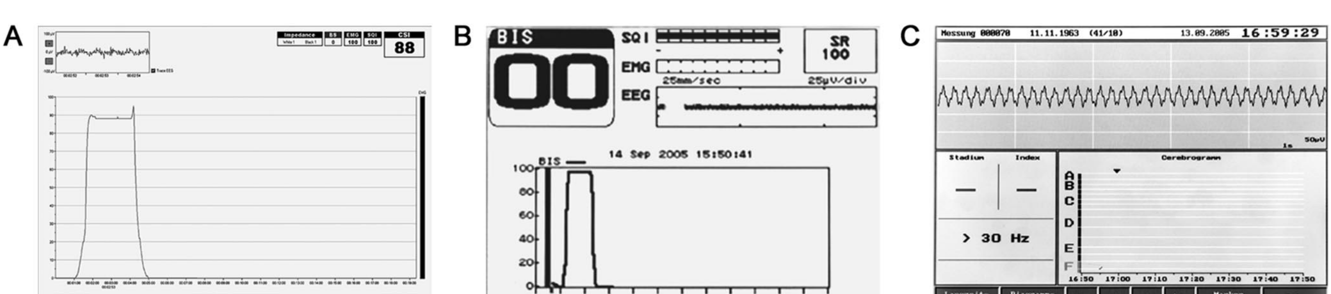

Fig. 2. Full-step approach: A full step from "deep anesthesia" to "awake" and back was given as input signal to the monitor: (*A*) Cerebral State Index (CSI), (*B*) Bispectral Index (BIS), (*C*) Narcotrend Index. When the full step was performed, the Narcotrend® monitor displayed "> 30 Hz" and no index value for more than 5 min.

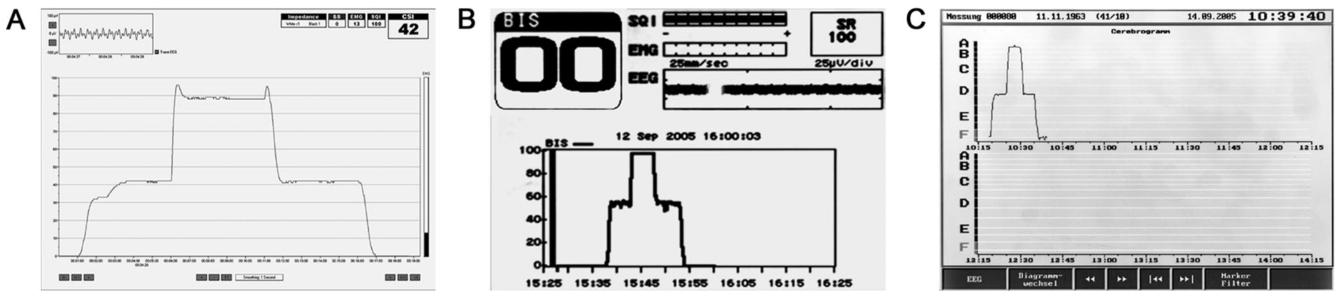

Fig. 3. Stepwise approach: In addition to the full-step approach, an intermediate level was added. We simulated a stepwise signal change from "deep anesthesia" to "general anesthesia," then from "general anesthesia" to "awake" and back: (*A*) Cerebral State Index (CSI), (*B*) Bispectral Index (BIS), (*C*) Narcotrend Index.

between the start of a new input signal and the display of the according index value. For BIS and NCT, latencies were measured using a digital stopwatch, because data can be obtained *via* the RS232 interface of these monitors only in 5-s intervals. These data were recorded in parallel on a personal computer.

We applied the following protocol to ensure that all possible transitions between the different levels of consciousness were registered. Each of the three signals was replayed until the according index value was reached and maintained for at least 1 min (time given in brackets).

1. Full increase/decrease: 0 → [1 min] → "awake" → [3 min] → 0
2. Stepwise approach: 0 → [1 min] → "general anesthesia" → [5 min] → "awake" → [5 min] → "general anesthesia" → [5 min] → 0
3. Small steps: 0* → step 1* → step 2* → step 3* → . . . * → CSI 100/BIS 98/NCT 93* → . . . * → step 3* → step 2* → step 1* → 0*

[* Each index value was maintained for 2–5 min.]

To avoid an electrode check during time measurement, which occurred every 5 min, the first input signal for the NCT was replayed for 7 min, and then the signals changed after 5 min each. Two repeated measurements were performed for each monitor. In both sequences, we achieved constant and identical index values with a high signal quality, and the time delays of index calculation showed comparable results at each transition.

Results

Analysis was planned for the calculation of time delay for CSI, BIS, and NCT values at the transition between the simulated signals:

1. Full-step approach: from "deep anesthesia" (CSI 0, BIS 0, NCT 5) to "awake" (CSI 89, BIS 98, NCT 94) and back
2. Stepwise approach: from "deep anesthesia" (CSI 0, BIS 0, NCT 5) to "general anesthesia" (CSI 42, BIS 52, NCT 46), then to "awake" (CSI 89, BIS 98, NCT 94) and *vice versa*

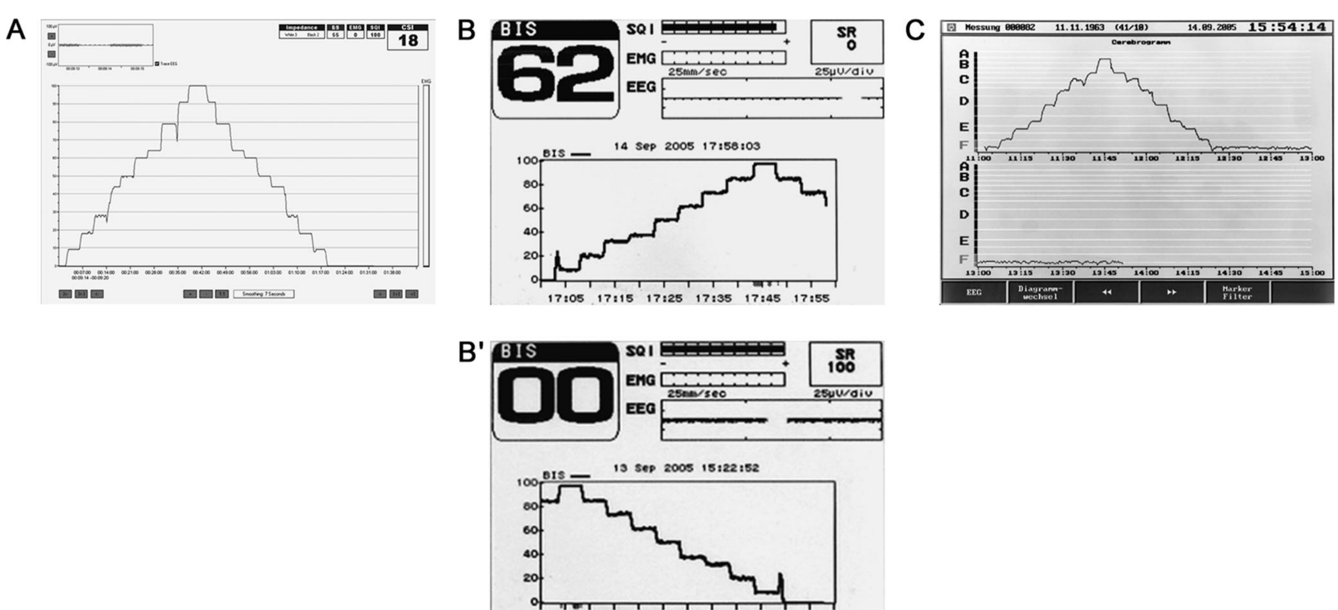

Fig. 4. Small steps: A sequence of signal changes between smaller index value steps was applied. (*A*) Cerebral State Index (CSI). (*B*) Bispectral Index (BIS), increasing values; (*B′*) BIS, decreasing values. (*C*) Narcotrend Index.

Table 1. Full-step Approach

Change of Input Signal	Time, s
CSI 0–90	54
CSI 0–89	64
CSI 89–95*	8
CSI 89–0	60
BIS 0–98	60
BIS 98–0	66
NCT 5–94	NA
NCT 94–5	45

The table shows the time delay (time) for index changes in the full-step approach. The left column shows baseline and target index values.

* Cerebral State Index (CSI) value at the overshoot.

BIS = Bispectral Index; NA = not applicable; NCT = Narcotrend Index.

3. Small steps: from lowest to highest index value and *vice versa*

The measured time delays for index calculation at each signal change are subdivided into results for increasing and decreasing index values and listed in tables 1–9.

Results for Increasing Index Values (tables 1, 2, 4, 5, and 6)

In the full-step approach, the CSM required between 54 and 64 s to adapt to the changed input signal (table 1). The time delay for the BIS was 60 s (table 1). For the NCT, no time delay could be determined (table 1). When the input signal was changed from "deep anesthesia" to "awake," the Narcotrend® monitor displayed "> 30 Hz" for more than 5 min. Therefore, the recording was discontinued.

Time delays during the ascending stepwise approach were between 15 and 155 s for the CSI, between 30 and 60 s for the BIS, and between 65 and 145 s for the NCT (table 2). When small steps were performed, calculation times were between 17 and 132 s for the CSI, between 18 and 59 s for the BIS, and between 20 and 60 s for the NCT (tables 4–6).

For increasing values, the CSI curve during the stepwise approach (fig. 3A) was exceptional. We revealed three specifics:

First, at the signal shift from CSI 0 to 42 after 133 s, the increasing CSI values reached and maintained a plateau at CSI 33 for approximately 40 s. Then, CSI values increased again until after 20 s a constant index value of 42 was reached (fig. 3A).

Second, we revealed an overshoot at transition from "general anesthesia" to "awake." At this transition, the CSI initially increased from 42 to 95 in 15 s, and then subsequently decreased to 89, the appropriate index value for the underlying signal, in a total of 45 s. With the full-step approach, a corresponding overshoot was seen at the signal change from CSI 0 to 89: The change from CSI 0 to a peak of CSI 90 was reached after 54 s, whereas a constant index value of 89 was obtained after 64 s (figs. 2 and 3).

Third, while performing "lightening of anesthesia" in small steps, a decline of CSI values at the change of input signals was observed twice: at the change from CSI 28 to 44 and from CSI 79 to 91 (fig. 4A). At the shift from 28 to 44, the CSI initially decreases to 24 within 12 s. This value is maintained for 1 s; subsequently, it increases to 28 in 12 s, and finally, the stable value of 44 is reached after a total of 72 s. At the signal change from CSI 79 to 91, the CSI initially decreases to 69 within 53 s. This value is maintained for 2 s, followed by an increase to the initial value of 79 in 10 s, and the target value of 91 is reached after a total of 90 s.

We were also able to detect an overshoot for the BIS in the small-steps protocol. When the input signal was

Table 2. Increasing Indices, Stepwise Approach

Change of Input Signal	Time, s
CSI 0–42	155
CSI 42–95	15
CSI 42–89	45
BIS 0–52	60
BIS 52–98	30
NCT 5–46	145
NCT 46–94	65

The table shows the time delay (time) for increasing index values with stepwise changes. The left column shows baseline and target index values.

BIS = Bispectral Index; CSI = Cerebral State Index; NCT = Narcotrend Index.

Table 3. Decreasing Indices, Stepwise Approach

Change of Input Signal	Time, s
CSI 89–95*	7
CSI 89–42	53
CSI 42–0	55
BIS 98–52	14
BIS 52–0	66
NCT 94–46	70
NCT 46–5	55

The table shows the time delay (time) for decreasing index values with stepwise changes. The left column shows baseline and target index values.

* Cerebral State Index (CSI) value at the overshoot.

BIS = Bispectral Index; NCT = Narcotrend Index.

Table 4. Increasing CSI, Small Steps

Change of Input Signal	Time, s
CSI 0–9	48
CSI 9–18	50
CSI 18–28	51
CSI 28–44	132
CSI 44–50	28
CSI 50–60	41
CSI 60–64	17
CSI 64–79	29
CSI 79–91	90
CSI 91–100	22

The table shows the time delay (time) for increasing Cerebral State Index (CSI) values with small step changes. The left column shows baseline and target CSI.

Table 5. Increasing BIS, Small Steps

Change of Input Signal	Time, s
BIS 0–25*	34
BIS 0–9	59
BIS 9–21	31
BIS 21–38	18
BIS 38–52	20
BIS 52–63	21
BIS 63–74	19
BIS 74–86	20
BIS 86–98	43

The table shows the time delay (time) for increasing Bispectral Index (BIS) values with small step changes. The left column shows baseline and target BIS and BIS value at the overshoot (*).

changed from BIS 0 to 9, the displayed index value increased to 25 in 34 s and then decreased to reach the target value of 9 in a total of 59 s (fig. 4B).

Results for Decreasing Index Values (tables 1, 3, and 7–9)

The change between extremes required 60 s for the CSI, 66 s for the BIS, and 45 s for the NCT. Time delays during stepwise changes were from 53 to 55 s for the CSI, from 14 to 66 s for the BIS, and from 55 to 70 s for the NCT. Using small steps, latencies ranged from 26 to 130 s for the CSI, from 15 to 66 s for the BIS, and from 15 to 66 s for the NCT. With both applied protocols (full-step and stepwise approach), an overshoot reaction was observed for the CSI: at transitions from "awake" to "general anesthesia" and from "awake" to "deep anesthesia." After switch from "awake" to "general anesthesia" or "deep anesthesia," both curves showed an increase from 89 to 95 within approximately 7 s (figs. 2 and 3). For the BIS, an overshoot was also observed in the small-steps protocol when the input signal was changed from BIS 9 to 0. First, the BIS increased to 25 in 28 s; then, it decreased to reach the target value of 0 in a total of 66 s (fig. 4B).

The overall fastest responses for each monitor were as follows: CSI: transition from "general anesthesia" (CSI 42) to CSI 95 after 15 s; BIS: transition from "awake" (BIS 98) to "general anesthesia" (BIS 52) after 14 s; NCT: transition from NCT 79 to 73 and from NCT 14 to "deep anesthesia" (NCT 0) after 15 s.

Table 6. Increasing NCT, Small Steps

Change of Input Signal	Time, s
NCT 5–14	30
NCT 14–23	25
NCT 23–31	30
NCT 31–46	60
NCT 46–61	45
NCT 61–73	55
NCT 73–79	35
NCT 79–93	20

The table shows the time delay (time) for increasing Narcotrend Index (NCT) values with small step changes. The left column shows baseline and target NCT.

Table 7. Decreasing CSI, Small Steps

Change of Input Signal	Time, s
CSI 100–91	130
CSI 91–79	26
CSI 79–64	66
CSI 64–60	53
CSI 60–50	58
CSI 50–44	41
CSI 44–28	70
CSI 28–18	51
CSI 18–9	56
CSI 9–0	61

The table shows the time delay (time) for decreasing Cerebral State Index (CSI) values with small step changes. The left column shows baseline and target CSI.

Discussion

The results of our study indicate that the response intervals of CSI, BIS, and NCT are not constant. With only one exception in the small-steps approach for each index, calculation times were different between decreasing and increasing index values. They also differed among the full-step, stepwise, and small-step approaches. The delay of time needed to calculate the indices depended on the particular starting and target index value.

In daily practice, this time delay is an important factor for the response time of a monitor, *e.g.*, in the detection of awareness. Increasing duration of responsiveness increases the risk of recall.[8,9] Intraoperative awareness with recall is seen as a rare phenomenon during general anesthesia with an incidence between 0.1 and 0.2%.[10,11] None of the current monitors can reliably predict awareness in advance. However, a monitor should at least be able to detect an awareness reaction. Dutton *et al.* [8,9] showed that an increasing time interval with wakefulness increases the probability of recall. In their study, the

Table 8. Decreasing BIS, Small Steps

Change of Input Signal	Time, s
BIS 98–86	18
BIS 86–74	17
BIS 74–63	20
BIS 63–52	16
BIS 52–38	21
BIS 38–21	18
BIS 21–9	15
BIS 9–25*	28
BIS 9–0	66

The table shows the time delay (time) for decreasing Bispectral Index (BIS) values with small step changes. The left column shows baseline and target BIS and the BIS value at the overshoot (*).

Table 9. Decreasing NCT, Small Steps

Change of Input Signal	Time, s
NCT 93–79	35
NCT 79–73	15
NCT 73–61	25
NCT 61–46	30
NCT 46–31	60
NCT 31–23	45
NCT 23–14	60
NCT 14–5	15

The table shows the time delay (time) for decreasing Narcotrend Index (NCT) values with small step changes. The left column shows baseline and target NCT.

critical event was wakefulness persisting for more than 30 s, whereas patients with shorter episodes of responsiveness did not have memories or recall after surgery. As a consequence, wakefulness should be detected with a minimal time delay. All available monitors need some time to indicate transitions from one level of anesthesia to another.

The current study discovered the existence of an overshoot at transition between "awake" and "general" or "deep anesthesia" and at transition between "general anesthesia" and "awake" for the CSI. As a consequence, too-high index values are indicated during imminent awakening. Therefore, the CSI indicates a higher level of consciousness than currently present. We consider this effect a tolerable limitation of the CSM. The overshoot at transition from "general anesthesia" to "awake" can be seen as an additional warning of patient's awareness.

In the small-steps approach, calculation time is longer for decreasing CSI values than for increasing values. The overshoot at transition from "awake" to "general anesthesia" and a slow detection of decreasing index values both bear the risk of a potential anesthetic overdose. This may occur when delayed or falsely high index values motivate the anesthesiologist to administer additional doses of anesthetics. For the BIS and the NCT, we could not detect a trend toward shorter time delays for increasing or decreasing index values in the small-steps approach. Both the BIS and the NCT showed markedly shorter time delays in the small-steps approach than the CSI.

Regarding the detection or prevention of awareness, the most relevant part of our study is the simulation of a sudden change from "general anesthesia" to "awake" (simulating a sudden awareness reaction, *e.g.*, induced by a painful stimulus). In the current study, the fastest response of the CSI was measured for values increasing from "general anesthesia" to "awake" (15 s from CSI 42 to 95). This indicates a fast response for detection of wakefulness and prevention of recall. BIS and NCT, however, showed time delays of 30 and 65 s, respectively, which might be too long, because wakefulness for more than 30 s increases the risk of recall.[9]

As mentioned above, the amount of time required to indicate a new level depended not only on the levels to be detected but also on the order in which these levels were applied, *i.e.*, the delay at the change from "awake" to "general anesthesia" was different from the delay at the change from "general anesthesia" to "awake," although identical electroencephalographic signals were used. This may indicate a limitation of these monitors for the use of pharmacodynamic modeling. For this purpose, electroencephalographic changes during ascending and descending drug concentrations are observed. These changes can be used to calculate pharmacodynamic parameters. Differences in the dose–response relation between the ascending and descending pathway are translated into pharmacodynamic parameters. As the current study indicates, there may be considerable differences between calculation times at increasing and decreasing index values. This is a potential source of erroneous pharmacodynamic results. We cannot rule out that differences in the algorithms for increasing and decreasing index values influence our results. However, as long as an index algorithm remains proprietary and information about the calculation times can not be given, it may not be the ideal tool for pharmacodynamic studies.

A potential limitation of the current approach is the use of simulated signals, because these signals may not completely resemble the electroencephalogram. However, the exact duration of calculation time cannot be measured in patients. With a bolus technique, the index decreases rapidly. The interval time from drug injection to the decrease of an index value is composed of two components: drug transition time (from injection site to the effect site) and the particular delay of time for index calculation. Interindividual differences of pharmacokinetics and pharmacodynamics cause huge interindividual variance of drug transition time and consequently make it impossible to substract this factor from the composed time interval. Therefore, we used artificially generated signals that produced constant index values. Another potential drawback of our approach is the immediate switch between the signals. This approach is artificial because *in vivo* drug-induced changes of the electroencephalogram occur gradually in a continuous way. Our protocol allowed an immediate change of the simulated "patient state" by switching from one input signal (with stable index value) to the next input signal (also with stable index value). As a consequence, the delay of time until the next index value is indicated is exclusively due to characteristics of the monitor, *i.e.*, calculation times.

As long as index algorithms are not accessible to the public, it remains unclear whether this delay is due to artifact detection algorithms or calculation of the index itself.

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