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Noxious Stimulation Response Index

A Novel Anesthetic State Index Based on Hypnotic–Opioid Interaction

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ABSTRACT

Background: The noxious stimulation response index (NSRI) is a novel anesthetic depth index ranging between 100 and 0, computed from hypnotic and opioid effect-site concentrations using a hierarchical interaction model. The authors validated the NSRI on previously published data.

Methods: The data encompassed 44 women, American Society of Anesthesiology class I, randomly allocated to three groups receiving remifentanil infusions targeting 0, 2, and 4 ng/ml. Propofol was given at stepwise increasing effect-site target concentrations. At each concentration, the observer assessment of alertness and sedation score, the response to eyelash and tetanic stimulation of the forearm, the bispectral index (BIS), and the acoustic evoked potential index (AAI) were recorded. The authors computed the NSRI for each stimulation and calculated the prediction probabilities (P_Ks) using a bootstrap technique. The P_Ks of the different predictors were compared with multiple pairwise comparisons with Bonferroni correction.

Results: The median (95% CI) P_K of the NSRI, BIS, and AAI for loss of response to tetanic stimulation was 0.87 (0.75–0.96), 0.73 (0.58–0.85), and 0.70 (0.54–0.84), respectively. The P_K of effect-site propofol concentration, BIS, and AAI for observer assessment of alertness and sedation score and loss of eyelash reflex were between 0.86 (0.80–0.92) and 0.92 (0.83–0.99), whereas the P_Ks of NSRI were 0.77 (0.68–0.85) and 0.82 (0.68–0.92). The P_K of the NSRI for BIS and AAI was 0.66 (0.58–0.73) and 0.63 (0.55–0.70), respectively.

Conclusion: The NSRI conveys information that better predicts the analgesic component of anesthesia than AAI, BIS, or predicted propofol or remifentanil concentrations. Prospective validation studies in the clinical setting are needed.

What We Already Know about This Topic

- The noxious stimulation response index has been proposed to predict, based on the effect-site concentrations of an opioid and an anesthetic, the likelihood of response to a noxious stimulus during anesthesia

What This Article Tells Us That Is New

- In data obtained from a previous study of 44 individuals, the noxious stimulation response index better predicted the response to noxious stimulation of the forearm than the bispectral index, although the bispectral index better predicted measures of sedation/hypnosis

THE cerebral effect of hypnotic drugs is frequently measured using processed electroencephalography with and without stimulation. During general anesthesia, opioids are administered according to response to clinical stimuli mostly in terms of arterial pressure or heart rate increase. Several indices measuring the balance between nociception and antinociception during general anesthesia are under investigation, but no "analgesic state index" is available predicting

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responsiveness to noxious stimulation during combined administration of an analgesic and a hypnotic.

In an attempt to develop an analgesic state monitor during anesthesia, we have investigated pulse wave and heart rate variation in response to a standardized electrical stimulus on the ulnar nerve as surrogate variable.[1–3] These variables were not related to predicted remifentanil effect-site concentrations. Conversely, the predicted remifentanil effect-site concentration combined with the bispectral index (BIS) was a significant predictor of a relevant hemodynamic response to tracheal intubation.[2] The prediction was not improved by adding the pulse wave response to electrical ulnar nerve stimulation.[2] Given the close correlation of the effect-site propofol concentration and the BIS,[4] we believe that the predicted effect-site propofol concentrations together with the predicted effect-site opioid concentrations and an appropriate interaction model provide sufficient information to predict the responsiveness of an anesthetized patient to noxious stimulation.

Bouillon *et al.*[5] have described a response surface model for propofol and remifentanil in 2004. The model is the basis for a two-dimensional concentration domain interaction display in which predicted hypnotic and opioid concentrations are related to interaction isoboles such as the 50 and 90% tolerance of laryngoscopy isobole. To present the same information in a time-domain display, Schumacher *et al.*[6] have defined the noxious stimulation response index (NSRI, see Methods section) based on the modified hierarchical interaction model by Bouillon.[7] Generally speaking, the NSRI is a univariate index calculated from the weighted propofol and remifentanil concentrations corrected for interaction and normalized to a range between 0 and 100, where 100 reflects 100% probability and values approaching 0 reflect close to 0% probability of responding to laryngoscopy.

The aim of this study was to compare the NSRI with predicted remifentanil and propofol effect-site concentrations, BIS, and A-Line autoregressive index (acoustic evoked potential index [AAI], A-Line AEP monitor, Danmeter A/S, Odense, Denmark) in terms of prediction probability (P_K) of the hypnotic state and the responsiveness to a noxious stimulus in anesthetized patients, using a previously published data set.[4]

Materials and Methods

Patients and Protocol of the Previous Study

In the previous study by Struys *et al.*,[4] 45 American Society of Anesthesiologists physical status 1 patients scheduled for ambulatory gynecologic surgery were enrolled and randomized to three treatment groups. Approval and written informed consent was granted for the original study by Institutional Ethics Committee of the Ghent University Hospital, Ghent, Belgium. The mean (SD) age in the three groups was 33 (5)–34 (4), and the mean weight and height were 63 (10)–66 (11) kg and 167 (6)–168 (6) cm, respectively. Propofol was infused in all groups according to a staircase protocol starting with effect-site target concentrations of 1.5 μg/ml in group 1 (no remifentanil) and 1.0 μg/ml in groups 2 and 3, in which remifentanil was added at effect-site target concentrations of 2.0 or 4.0 ng/ml, respectively. The infusion pumps were controlled by Rugloop II software (Demed, Temse, Belgium) using the pharmacokinetic parameter sets and effect-site equilibration constant (ke0) reported by Schnider *et al.*[8,9] for propofol and Minto *et al.*[10,11] for remifentanil.

Propofol concentration was increased in steps of 0.5 μg/ml every 4 min. After an effect-site equilibration time of 4 min, that is, immediately before the next increase of the propofol target concentration, the eyelash reflex, the observer assessment of alertness and sedation score (OAAS), the BIS (Version 3.4, calculated by the A-2000 BIS® monitor, Aspect Medical Systems, Newton, MA), the AAI, and the propofol effect-site concentration were recorded. Thereafter, the presence or absence of a motor response to a 2-s tetanic stimulus (100 Hz, 50 mA) applied on the volar forearm was recorded. In the raw data set, the predicted propofol and remifentanil effect-site concentrations and the related eyelash reflex (present or absent), OAAS score, BIS, AAI, and response to tetanic stimulation were available.

The Hierarchical Propofol–Remifentanil Interaction Model

The NSRI is based on the hierarchical interaction model by Bouillon *et al.*[5] in 2004. The originally reported model was modified to increase parsimony while retaining its essential features (appendix).[7] On the basis of this modified model, the combination of predicted propofol and remifentanil concentrations can be expressed as probability to tolerate a certain reference stimulus, for example, tolerance of "shaking and shouting," as indicator of deep hypnosis. The original and the modified model are illustrated in figure 1.

1. Reduction of the incoming stimulus intensity:

$$\text{postopioid\_intensity} = \text{preopioid\_intensity}\left(1 - \frac{\text{Ce}_{\text{opioid}}}{\text{Ce50}_{\text{opioid}} + \text{Ce}_{\text{opioid}}}\right) \quad (1)$$

where postopioid_intensity = stimulus intensity after attenuation by the opioid, preopioid_intensity = intensity of the incoming stimulus, Ce_{opioid} = effect-site opioid concentration, and $Ce50_{opioid}$ = effect-site opioid concentration associated with a 50% reduction of preopioid_intensity. Therefore, the $Ce50_{opioid}$ does not represent the opioid concentrations associated with half maximal effect on the probability of tolerating the stimulus but it is the ability to increase the effectiveness of the hypnotic by altering the respective Ce50 of the hypnotic ($Ce50_{hyp}$, see Eq. 2). For a single stimulus, preopioid_intensity must be set to 1 to identify the C50 of the hypnotic (see Eq. 2). In this case, the postopioid_intensity is always a dimensionless number between 0 and 1, depending on the opioid concentration.

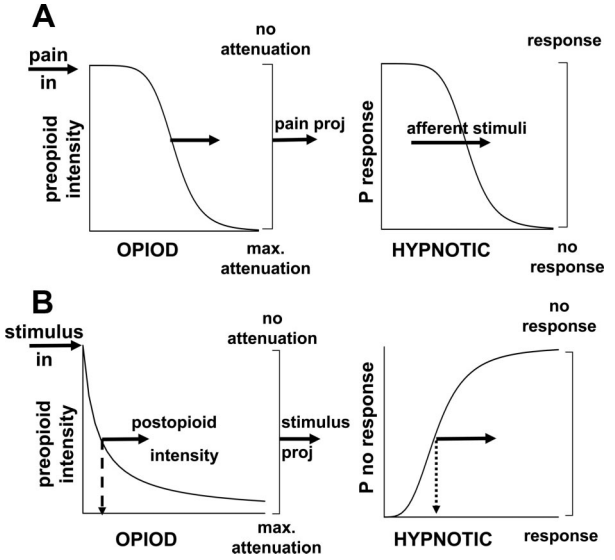

Fig. 1. Comparison of the original and the modified hierarchal opioid–hypnotic interaction model. The endpoint of the opioid–hypnotic interaction is the probability of response ($P_{response}$, original model, *A*) or nonresponse to a stimulus ($P_{nonresponse}$, modified model, *B*). The incoming stimulus is attenuated by the presence of an opioid. $P_{response}$ or $P_{nonresponse}$ is dependent on the strength of the attenuated stimulus, the hypnotic drug concentration, and the hypnotic drug concentration associated with a 50% probability of response/nonresponse ($C50_{hypnotic}$). In the original model (*A*), the incoming stimulus (= "pain in") of a strength-labeled preopioid_intensity on the y-axis is attenuated by the opioid (on the x-axis) according to a negative Emax model resulting in an afferent stimulus with a strength that is a fraction of preopioid_intensity. The preopioid stimulus intensity and the slope parameter of this Emax model are estimated from the data. The projected pain ("pain proj") refers to the intensity of the attenuated stimulus transmitted to the central nervous system (also labeled as "afferent stimuli" in the original model). $P_{response}$ is estimated from a negative Emax model. In the modified model (*B*), the terms pain in and pain proj are replaced by "stimulus in" and "stimulus proj," respectively because unconscious anesthetized patients do not feel pain. Attenuation of preopioid_intensity follows a fractional Emax model with a fixed slope constant of 1. The $C50_{opioid}$ (dashed arrow) is the opioid concentration reducing the strength of preopioid_intensity by 50%. $P_{nonresponse}$ is estimated with a positive Emax model, including the parameters postopioid_intensity, current hypnotic drug concentration (x-axis), and the $C50_{hypnotic}$ (dotted arrow). Supplemental Digital Content 1 illustrates the behavior of the modified model, http://links.lww.com/ALN/A578 (for further information refer to the appendix).

2. Calculation of probability of tolerance to an incoming stimulus: the postopioid_intensity modifies the $Ce50_{hyp}$ representing the hypnotic concentration that corresponds to a 50% probability of tolerance of a stimulus with preopioid_intensity in the absence of opioid.

$$P_{\text{no-response}} = \frac{\left(\frac{Ce_{hyp}}{Ce50_{hyp} \cdot \text{postopioid\_intensity}}\right)^{\phi}}{1 + \left(\frac{Ce_{hyp}}{Ce50_{hyp} \cdot \text{postopioid\_intensity}}\right)^{\phi}} \quad (2)$$

where $P_{no\text{-}response}$ = probability of nonresponse to a stimulus, Ce_{hyp} = effect-site concentration of hypnotic, and ϕ = slope parameter.

In summary, the model expresses the probability of nonresponse to a stimulus as a function of the stimulus strength (as incorporated in postopioid_intensity) and the opioid and hypnotic drug concentrations. The modified model is depicted in figure 1B (for further details see the appendix). The mechanistic behavior of the model is further illustrated in Supplemental Digital Content 1, which contains an interactive excel worksheet for model simulation, http://links.lww.com/ALN/A578.

3. Extension to stimuli of differing intensity: Under the assumption that the opioid potency ($C50_{opioid}$) is identical for fractional suppression of stimuli of differing strength, only one parameter has to be added per additional stimulus, either "preopioid_intensity of $stimulus_n$" (n = suffix for the nth stimulus) or, alternatively, the model can be parameterized with "$C50_{hyp\ n}$" (n = suffix for the $C50_{hyp}$ related to the nth stimulus). If the second parameterization is chosen, the ratio of the respective C50s yields the relative strength of the stimuli. The second parameterization was chosen with "shake and shout" as reference stimulus with a preopioid_intensity of 1. The relative intensity of laryngoscopy then corresponds to the ratio of the propofol $Ce50_{TOSS}$ and the $Ce50_{TOL}$ (Eq. 3).

$$R_{lar} = \frac{Ce50_{hypTOL}}{Ce50_{hypTOSS}} \quad (3)$$

where R_{lar} = intensity ratio of laryngoscopy to the calibration stimulus shaking and shouting, $Ce50_{hypTOL}$ and $Ce50_{hypTOSS}$ = effect-site hypnotic concentrations associated with 50% probability of tolerating laryngoscopy and shake and shout, respectively. The parameter estimates (SE) for $Ce50_{hypTOL}$ and $Ce50_{hypTOSS}$ according to the modified model were 8.46 (1.98) and 2.99 (0.75) $\mu g/ml^{-1}$, respectively. Intensity ratios compared with shake and shout can be computed for any other stimulus, provided the respective $Ce50_{hyp}$ is known.

Transformation of Probabilities of Tolerance into NSRI Units.

1. The combined potency of an opioid and a hypnotic for suppression of a stimulus of defined strength (N) can be expressed as:

$$N = \frac{Ce_{hyp}}{Ce50_{hyp} \times \text{postopioid\_intensity}} \quad (4)$$

Therefore, equation 2 can be generalized according to equation 5.

$$P_{\text{no-response}} = \frac{N^{\phi}}{1 + N^{\phi}} \quad (5)$$

2. The probability of no-response to laryngoscopy (P_{TOL}) can be computed according to equations 3 and 5.

$$P_{TOL} = \frac{(N/R_{lar})^{\phi}}{1 + (N/R_{lar})^{\phi}} \quad (6)$$

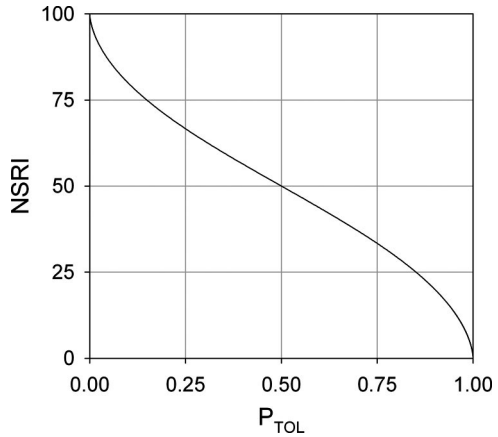

Fig. 2. The relation of the probability to tolerate laryngoscopy and noxious stimulation response index (NSRI). The NSRI is calculated using the same structural model as the probability to tolerate laryngoscopy (P_{TOL}) but with a modified slope constant. The figure related the P_{TOL} to corresponding NSRI values. An NSRI of 50 and 20 corresponds to 50% and 90% probability of tolerating laryngoscopy, respectively. The shape of the curve is dependent on the slope constant.

3. Normalization to a scale from 0 to 100 and calibration: for ergonomic reasons (conformity with standard electroencephalographic monitoring), the increasing probability of tolerating laryngoscopy (scale from 0 to 1) with increasing drug concentrations was transformed into a decreasing value from 100 (probability of no-response to laryngoscopy = 0) to 0 (probability of no-response to laryngoscopy asymptotically approaching 1) by transformation and by modifying the slope parameter of equation 6. The NSRI value can therefore decrease near 0 but never be exactly 0. By using the same structural model as for the probability of no-response to laryngoscopy, the NSRI is defined as follows.

$$\mathrm{NSRI} = 100 \times \left(1 - \frac{(\mathrm{N}/R_{\mathrm{lar}})^{\mathrm{sl}}}{1+(\mathrm{N}/R_{\mathrm{lar}})^{\mathrm{sl}}}\right) \qquad (7)$$

where slope factor sl is an empirically calibrated scalar and not an estimated model parameter or a mathematical transformation of the slope parameter ϕ. Regardless of the value of sl, a P_{TOL} of 0.5 corresponds to a NSRI of 50. The slope factor sl was calibrated to transform a P_{TOL} of 0.9 to an NSRI of 20, yielding sl = 2.18. The NSRI has the same underlying structural model but is not a direct mathematical transformation of P_{TOL}. The relationship between the NSRI and the probability of tolerance of laryngoscopy is depicted in figure 2.

Data Evaluation and Statistics

The predicted propofol and remifentanil effect-site concentrations from the previous study[4] were used to compute the related NSRI according to equations 1, 4, and 7.

For comparison, P_{TOL} was calculated according to equations 1 and 2. Primary independent variables (= predictors) were the NSRI and the predicted propofol and remifentanil effect-site concentrations. Primary dependent variables were the modified OAAS (full scale, table 1), the presence or absence of the eyelash reflex, and the presence or absence of a motor response to electrical tetanic stimulation of the forearm (dichotomous), BIS, and AAI values (continuous data). The BIS and the AAI were also used as predictors of OAAS and response to eyelash and tetanic stimulation. A similar analysis was performed for P_{TOL}.

Table 1. Modified Observer Assessment of Alertness and Sedation Score as Applied by Struys *et al.*[4]

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly an/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

For all predictors, the P_Ks for all variables to be predicted were calculated. The prediction probability macro (PKMACRO; Excel spreadsheet) developed by Smith *et al.*,[12] which was used for data evaluation in the previous article,[4] is designed for analysis of independent data. Because the data were not independent, we applied a bootstrap technique with 1,000 random samples of the 263 data points for each dependent variable for P_K calculation using Matlab (The Mathworks Inc., Natick, MA). Each sample included one random data point per patient, that is, 44 data points. The P_K value was then calculated for each sample using the PKMACRO functionality within Matlab. With this modification, the assumption of independence of the data was not violated. Because the P_K values were not normally distributed, they are presented in box plots. To avoid assumptions on the distribution of the bootstrap samples, the 2.5–97.5 percentile range of the 1,000 P_K was calculated to approximate the 95% CI of the resampled P_Ks. The differences between a median P_Ks of a given predictor (*e.g.*, NSRI) and another predictor (*e.g.*, BIS) in predicting the same variable (*e.g.*, OAAS) were considered statistically significant if the median P_K of the first was outside the 95% CI of the second predictor, corresponding to an [*alpha*] of 0.05. Because statistical testing with calculation of *P* values might be affected by the bootstrap distribution and the number of resamplings, we restrict our P_K comparison to this rather crude and conservative method and do not present the calculated *P* values.

To get a rough estimate of the intensity of the 2-s tetanic stimulation, the NSRI associated with a 50% probability of loss or response to tetanic stimulation was calculated using a simple logistic regression analysis in NONMEM (Version V, Globomax LLC, Hanover, MD). The naïve pooled data method was applied for parameter estimation. Patient identifier, NSRI, dependent variable (0 or 1), and missing dependent variable (0 or 1) were the input data. No further model building steps were performed, and no covariates were evaluated.

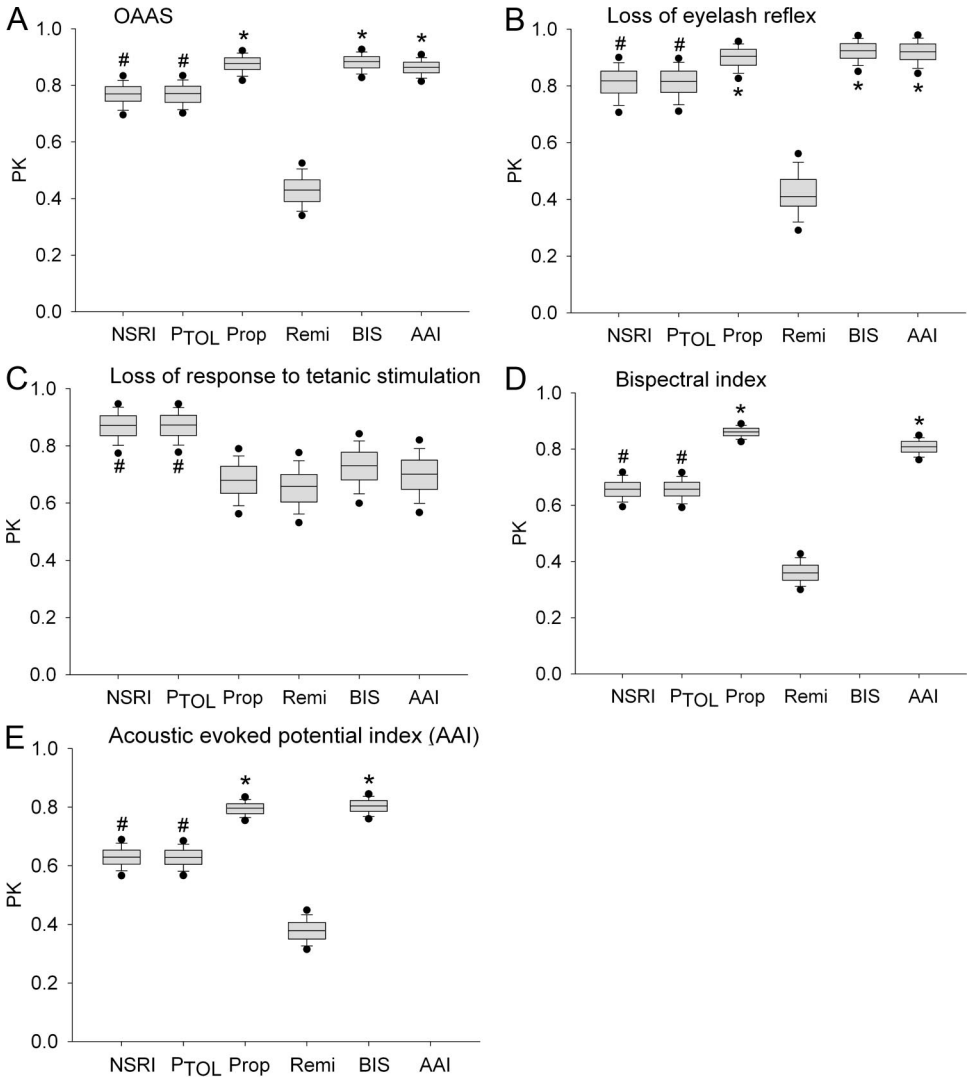

Fig. 3. Prediction probabilities (P_Ks) of different predictors and predicted variables. The P_K values according to Smith *et al.*[12] were estimated from 1,000 random samples of 263 data points from 44 patients, with 1 data point per patient in each sample. The data are presented as *box plots* with median values depicted as *horizontal lines* and the interquartile range (*lower* and *upper limits of the boxes*). The *error bars* represent the 10 and 90 percentiles, and the *black circles* the 5 and 95 percentiles. Pairwise comparison of the P_K values by comparing the median P_K of one predictor with the 2.5–97.5 percentile range of another predictor (corresponding to the 95% confidence interval). If the median P_K of the first is outside this percentile range, it is considered significantly different. *A*: observer assessment of alertness and sedation score (OAAS), *B*: loss of eyelash reflex, *C*: loss of motor response tetanic stimulation, *D*: bispectral index (BIS), and *E*: acoustic evoked potential index (AAI).* = Significantly different compared with noxious stimulation response index (NSRI), probability to tolerate laryngoscopy (P_{TOL}), and effect-site remifentanil concentration (Remi); # = Significantly different compared with effect-site propofol concentration (Prop), BIS, AAI, and Remi.

Results

The data of one patient were incomplete; hence, 263 data sets of 44 patients were available for our reanalysis.

The dependent variables loss of eyelash reflex, BIS, and AAI reflect the hypnotic state, whereas loss of response to tetanic stimulation reflects the analgesic state. The OAAS is mostly used as a clinical measure of the hypnotic state and dominated by hypnotic surrogate endpoints; however, the discrimination between levels 1 and 0 is based on the response to a painful stimulus (trapezius squeeze). The results of the P_K analysis are presented in figure 3.

The P_K values (95% CI) for prediction of OAAS by the effect-site propofol concentration, the BIS, the AAI, and the NSRI were 0.88 (0.81–0.93), 0.88 (0.82–0.93), 0.86 (0.80–0.92), and 0.77 (0.68–0.85), respectively.

The P_K values of NSRI, effect-site propofol concentration, BIS, and AAI for prediction of loss of response to tetanic stimulation were 0.87 (0.75–0.96), 0.68 (0.54–0.81), 0.73 (0.58–0.85), and 0.70(0.54–0.84), respectively, whereas the corresponding P_K of the remifentanil effect-site concentration was 0.66 (0.50–0.80). The reason for the median propofol P_K being slightly higher than the remifentanil P_K might be explained by the study design including only two remifentanil concentrations.

The P_Ks of the remifentanil effect-site concentration to predict OAAS, loss of eyelash reflex, BIS, and AAI were 0.43

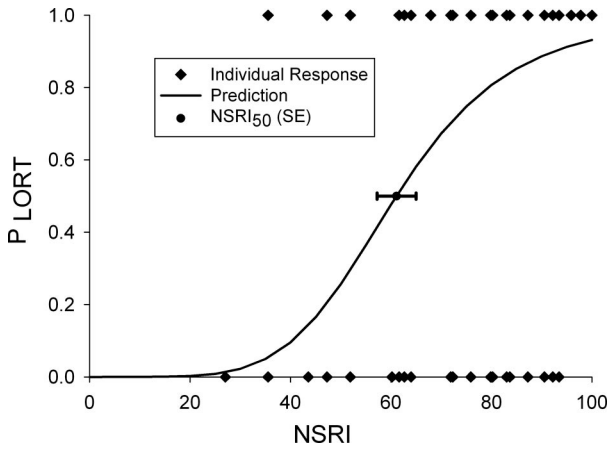

Fig. 4. The $NSRI_{50}$ for tolerance of 2-s tetanic stimulus: A logistic regression analysis with the naïve pooled data method (non-linear mixed effects modeling naïve pooled analysis) for dependent variables was performed to estimate the noxious stimulation response index (NSRI) value associated with a 50% probability to tolerate tetanic stimulation of the forearm (= $NSRI_{50}$). P_{LORT} = probability of tolerance of tetanic stimulation; *black diamonds* = individual response to tetanic stimulation (1 = response and 0 = no response); prediction (*black line*) = predicted probability of response according to the regression model; *black circle* = NSRI associated with P_{LORT} = 50%; error bars = standard error of the estimate.

(0.32–0.54), 0.41 (0.26–0.59), 0.36 (0.29–0.45), and 0.38 (0.30–0.46), respectively, which indicates a slight reverse prediction, most likely caused by study design (in groups with remifentanil, the propofol concentrations were lower).[4] The P_K for P_{TOL} was similar to NSRI (fig. 3B) because the NSRI is the transformed and rescaled P_{TOL}. The NSRI (SE of the estimate) associated with a 50% probability of loss of response to tetanic stimulation was 61 (SE, 3.8) (fig. 4).

Discussion

The NSRI integrates the potency of a hypnotic and an opioid to synergistically suppress the response to a noxious stimulus. In this study, we have shown that the P_K of the NSRI and P_{TOL} to predict the probability of response to a 2-s, 50-mA, 100-Hz tetanic stimulus is higher compared with all other investigated predictors. As expected, the P_K of the mainly hypnotic endpoints (loss of eyelash reflex and OAAS) was intermediate, and the P_K of electroencephalogram-based predictors (BIS and AAI) was low.

The predictive performance of propofol effect-site concentrations, BIS, and AAI to predict loss of consciousness in our study was as high as in a previous study in which P_Ks of 0.89–0.94 were reported.[13] The performance in predicting a response to noxious stimulation with these variables was 0.82–0.87 with pure propofol anesthesia[13] and 0.72–0.75 with coadministration of remifentanil.[4] These findings reflect the poor sensitivity of electroencephalogram-based measurements to the effect of opioids.

Surrogate endpoints potentially reflecting the analgesic state have been investigated. The surgical stress index uses the pulse plethysmography amplitude and the pulse rate derived from the pulse oximetry curve and discriminates strong *versus* light stimulation and low *versus* moderate remifentanil effect-site concentrations.[14] The skin conductance variation induced by several noxious and nonnoxious stimuli is a sensitive measure of stress[15,16] but discriminates only between the presence or absence of low remifentanil effect-site concentrations (2 ng/ml).[16] Whether it discriminates different opioid concentration levels or predicts the response to clinical stimuli is not known. Our investigations of the pulse plethysmography response to a 5-s 60-mA tetanic stimulus of the ulnar nerve as a surrogate variable to measure the analgesic state or the hemodynamic responsiveness of anesthetized patients were disappointing.[1,2] One reason was the large and probably random interindividual variation[1] of the signal (tetanic stimulation-induced variation of the pulse plethysmography trace). Therefore, we assume that baseline variability may reduce the predictive performance of any analgesic state index that is derived from physiologic signals related to the sympathoadrenergic stress response. Because the NSRI takes into account predicted effect-site drug concentrations and their interaction only, these drawbacks do not apply. It seems that the prediction error of effect-site drug concentrations, which is greater or equal to 20%,[8,10] does not degrade the prediction performance of the NSRI. Because the NSRI accounts for the interaction of hypnotic and analgesic, it must be superior to single drug concentrations for prediction of any endpoint for which hypnotic/analgesic interactions have been demonstrated, that is, responsiveness to noxious stimuli during anesthesia.

In summary, the strengths of the NSRI are a predictive performance for noxious stimulation response in the clinically desirable range and its independence of physiologic signals as well as test stimuli. As with other anesthetic depth indicators or drug concentrations, the predictive performance expressed as P_K does not imply that a given NSRI value correctly predicts the response in an individual patient, but it means that the probability of response is highly correlated with the NSRI. The calibration of NSRI and P_{TOL} as anesthetic depth indicators was beyond the scope of this study and needs to be prospectively evaluated.

Because of the modification of the underlying hierarchical interaction model, the index is flexible for future development so that it can be extended to any combination of hypnotic and analgesic drugs. A discussion of the model modification is provided in the appendix. The interpretation of the NSRI numbers is straightforward. By definition, an NSRI of 50 means that the effect-site propofol and remifentanil concentrations are sufficient that the patient will tolerate laryngoscopy with a probability of 50%. An NSRI of 61 (3.9) means that the patient will tolerate a 2-s tetanic stimulus of the forearm with a probability of 50% and that this stimulus may be slightly weaker than laryngoscopy. Different probabilities for responses to different stimuli can be mapped on the curve with ease. Clinically desirable ranges of the

NSRI during surgery can be inferred from the results of a future proof of concept study.

When the PKMACRO (calculating the P_K of a single predictor to one predicted variable) and the predition probability difference macro (PKDMACRO) (comparing the P_Ks of different predictors) were used for validation of anesthetic depth indicators in the past, the assumption on independence of the data has been neglected. The reason for this is inherent in the study design with repeated measurements taken at several drug concentrations in the same subject. The resampling technique applied in this study is an attempt to solve this problem of the statistical analysis. Currently, it is not clear how far the resampling method affects the boundaries of our parameter estimates and to what extend a sampling bias could have been introduced. To clarify this, a formal evaluation of this technique under a range of circumstances in which the "true" bounds are known would be required, which is well beyond the scope of this study. Therefore, we have presented the 2.5–97.5 percentile ranges of the different P_Ks that approximate the 95% CIs and did not calculate any *P* values. To reject the null hypothesis that two P_Ks are similar, the median P_K of one predictor had to be outside the 95% CI of P_Ks of the other. Therefore, only large differences in the median P_Ks were accepted as significant, which are unlikely to be substantially affected by a potential sampling bias; for example, the difference between the P_Ks of NSRI and P_{TOL} and the P_Ks of all other predictors to predict response to a noxious stimulus (fig. 3). It is, therefore, unlikely that the main message of this study is affected by this yet unsolved statistical problem.

There are some other limitations of this study. First, it is a *post hoc* validation. Second, the selected propofol and remifentanil concentrations are not independent of each other. Third, the applied 2-s tetanic stimulus is substantially weaker than strong surgical stimuli such as skin incision,[17] which is illustrated by the high $NSRI_{50}$ for loss of response to tetanic stimulation. Fourth, the data used for this validation were recorded only in a female patient population. Therefore, this study only attests to the usefulness of the NSRI as predictor of the response to medium-intensity stimuli during coadministration of propofol and remifentanil. Future studies have to validate the NSRI in the clinical setting for both total intravenous and balanced (volatile plus opioid) anesthesia and in both sexes.

We conclude that the NSRI is a promising anesthetic state index predicting response to noxious stimulation responsiveness and, to a lesser extent, the hypnotic state. Most probably, it will improve the dosing of hypnotics/volatiles and opioids. However, prospective validation studies in the clinical setting are needed to judge the use of the NSRI in everyday anesthetic practice.

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Appendix: Modification of the Hierarchical Interaction Model

In this appendix, the steps of model modification as reported by Bouillon[7] are described. The original model[5] was modified to avoid overparameterization. The resulting modified model was found to be mathematically equivalent to a reduced Greco model, implying strong synergism. Its C50 for the opioid can be interpreted in analogy to a C50 for reduction of the minimal alveolar concentration of a volatile anesthetic.

Model Modifications

The probability of response to a stimulus is a function of stimulus strength after attenuation by the opioid (postopioid_intensity), the $C50_{hypnotic}$, the slope factor, and the concentration of the hypnotic. As is evident from equation A,[5] only the product of $Ce50_{hypnotic}$ and postopioid_intensity, but not its individual components, is identifiable (Eq. A).

$$P_{responsiveness} = 1 - \frac{Ce_{hypnotic}^{\phi}}{Ce_{hypnotic}^{\phi} + (Ce50_{hypnotic} * postopioid\_intensity)^{\phi}} \quad \text{(A)}$$

where $P_{responsiveness}$ = probability that the patient responds to the incoming stimulus, $Ce_{hypnotic}$ = effect-site hypnotic drug concentration, $Ce50_{hypnotic}$ = effect-site hypnotic drug concentration associated with a 50% probability of nonresponsiveness, and ϕ = slope parameter.

In the absence of opioid, postopioid_intensity equals preopioid_intensity, as shown in equation B.

$$postopioid\_intensity = \ldots preopioid\_intensity * \left(1 - \frac{Ce_{opioid}^{\gamma}}{(Ce50_{opioid} * preopioid\_intensity)^{\gamma} + Ce_{opioid}^{\gamma}}\right) \quad \text{(B)}$$

where preopioid_intensity = intensity of the incoming stimulus, Ce_{opioid} = effect-site opioid concentration, $Ce50_{opioid}$ = the common opioid concentration reducing the intensity of an incoming stimulus by 50%, and gamma (γ) = slope parameter.

From this, it follows that stimulus strength cannot be estimated *per se*, if only one stimulus is investigated and preopioid_intensity must be fixed to 1 to obtain the C50 of the hypnotic. For n stimulus strengths, the number of parameters describing stimulus strength equals n − 1. These parameters describe relative strength of stimulus compared with the reference stimulus with the intensity of 1. Alternatively, the model can be parameterized in terms of one C50 for the hypnotic per stimulus applied.

The model describing postopioid_intensity was also simplified. Because the original estimate of the slope factor almost equaled 1, the model was collapsed to a fractional Emax model. In the original model, the multiplication of the C50 of the opioid with the preopioid pain intensity was believed to be necessary to account for the fact that higher opioid concentrations are needed to attenuate more severe pain. Although not obvious, this behavior is also displayed by the modified model (Eq. C).

$$\text{postopioid\_intensity} = \text{preopioid\_intensity} * \left(1 - \frac{Ce_{opioid}}{Ce50_{opioid} + Ce_{opioid}}\right) \quad \text{(C)}$$

It is therefore the absolute value of postopioid_intensity and the C50 hypnotic that determine the concentration of hypnotic needed to achieve a certain probability of nonresponsiveness for a certain preopioid stimulus strength.

We would like to further illustrate this with a straightforward example.

i. Simplest case: preopioid stimulus intensity = 1, $Ce_{opioid} = 0$, and $P_{nonresponsiveness} = 0.5$. The Ce_{hyp} equals the C50 of the hypnotic.
ii. Add opioid to decrease Ce_{hyp} for $P_{nonresponsiveness} = 0.5$ by 50%. The Ce_{opioid} that lowers the preopioid_intensity from 1 to a postopioid_intensity of 0.5 equals the $Ce50_{opioid}$ (Eqs. B and C).
iii. Add opioid to decrease Ce_{hyp} for $P_{nonresponsiveness} = 0.5$ by 50%, for another stimulus with preopioid_intensity of 2. According to equation B (original model), the $Ce_{opioid} = 6 \times Ce50_{opioid}$, whereas according to equation C (modified model), the $Ce_{opioid} = 3 \times Ce50_{opioid}$.

Therefore, the most simplified equation C already predicts a profound increase of the opioid concentration needed to attenuate stimulus intensities higher than 1. A simulation spreadsheet is provided in Supplemental Digital Content 1, http://links.lww.com/ALN/A578.

The following parameter estimates (SE) were obtained in a reanalysis of the data from the previous study[5]: $Ce50_{propofol,\ TOSS}$ = 2.99 (0.75) μg/ml, $Ce50_{propofol,\ TOL}$ = 8.46 (1.98) μg/ml, and $Ce50_{remifentanil,\ TOSS}$ = 1.16 (0.48) ng/ml, whereas the $Ce50_{remifentanil,\ TOL}$ is implicitly modeled and not estimated from the data. The non-linear mixed effects modeling objective function was 80.2.

Discussion

When we reanalyzed the data from the original study,[7] the non-linear mixed effects modeling objective function value of the modified hierarchical model and the Greco model was equal, whereas it was 69 in the original model.[5] However, the small SEs of the parameter estimates in the original model are indicators of overparameterization.

Furthermore, the rather high Ce50 of propofol for hypnosis (4.82 μg/ml) does not compare well with results from other studies[18,19] and clinical experience. In contrast, the $C_{50,\ propofol}$ for tolerance of shaking and shouting (corresponding to the $C_{50,\ propofol}$ for loss of consciousness) estimated with the modified model was 2.99 μg/ml, which is well within the range of published data.[13,19,20]

A structural benefit of the model is the ability to convert it into a reduced Greco model,[7] simplifying comparisons with existing studies. The $C_{50,\ opioid}$ in our model equals the reciprocal ϵ' of that model according to equation D.

$$C_{50,\ opioid} = \frac{1}{\epsilon'} \quad \text{(D)}$$

where $C_{50,\ opioid}$ = opioid concentration associated with half maximal attenuation of a stimulus in our model and ϵ' = the modified Greco interaction parameter for constellations in which the opioid effect in the absence of hypnotic is too weak to be identified but profoundly changes the potency of a coadministered hypnotic. This situation was encountered in the interaction study by Mertens *et al.*[19] The proof of interconvertability of the two models has been described elsewhere.[7] Interestingly, the $Ce_{50,\ remifentanil}$ estimated with the simplified Greco model from the propofol–remifentanil interaction data is 1.39 and 1.45 ng/ml for return of consciousness and for tolerating laryngoscopy, respectively, which is almost identical despite completely different stimulation strength and approximates the $C_{50,\ remifentanil}$ estimated with our modified hierarchical model (1.16 ng/ml).

The model for the probability of nonresponse in this study was, therefore, parametrized according to equation E.

$$P_{non-response} = \frac{\left(\frac{Ce_{hypnotic}}{Ce50_{hypnotic} \cdot preopioid\_intensity * \left(1 - \frac{Ce_{opioid}}{Ce50_{opioid} + Ce_{opioid}}\right)}\right)^{\phi}}{1 + \left(\frac{Ce_{hypnotic}}{Ce50_{hypnotic} \cdot preopioid\_intensity * \left(1 - \frac{Ce_{opioid}}{Ce50_{opioid} + Ce_{opioid}}\right)}\right)^{\phi}} \quad \text{(E)}$$

where $P_{nonresponse}$ = probability of tolerance of a given stimulus, $Ce_{hypnotic}$ = effect-site hypnotic drug concentration, $Ce50_{hypnotic}$ = effect-site hypnotic drug concentration associated with a 50% probability of nonresponse, preopioid_intensity = intensity of the stimulus without opioid attenuation, $Ce50_{opioid}$ = effect-site opioid drug concentration reducing the preopioid_intensity by 50%, and Ce_{opioid} = effect-site opioid concentration.

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