ORIGINAL ARTICLE

Prediction of hemodynamic reactivity during total intravenous anesthesia for suspension laryngoscopy using Analgesia/Nociception Index (ANI): a prospective observational study

E. BOSELLI [1, 2], L. BOUVET [1], G. BÉGOU [1], S. TORKMANI [1], BERNARD ALLAOUCHICHE [1, 2]

[1]Department of Anesthesiology and Intensive Care, Édouard Herriot hospital, Hospices Civils de Lyon, Lyon, France; [2] Claude Bernard Lyon I University, University of Lyon, Lyon, France

ABSTRACT

Background. The Analgesia/Nociception Index (ANI), a 0-100 non-invasive index calculated from heart rate variability, reflects the analgesia/nociception balance during general anesthesia. The principal objective of this study was to evaluate the performance of ANI to predict hemodynamic reactivity during suspension laryngoscopy. The secondary objectives were to investigate the performances of ANI and bispectral index (BIS) to assess sedation and of BIS to predict hemodynamic reactivity during the procedure.

Methods. Fifty patients undergoing suspension laryngoscopy with total intravenous anesthesia using propofol and remifentanil were analysed in this prospective observational study. The ANI, BIS and Observer's Assessment of Alertness/Sedation (OAA/S) scale were measured at predefined time-points during the procedure. Receiver-operating characteristic (ROC) curves were built to evaluate the performance of ANI and BIS to predict hemodynamic reactivity (increase by more than 20% of heart rate and/or systolic blood pressure within 5 min) and assess sedation (OAA/S≤2) during the procedure.

Results. For the prediction of hemodynamic reactivity, better performance was observed with ANI in comparison to BIS (ROC curve AUC [95% CI]=0.88 [0.83-0.92] *vs.* 0.73 [0.66-0.79], P<0.05). The sensitivity and specificity of ANI ≤55 to predict hemodynamic reactivity within 5 min were 88% and 83%, respectively. For the assessment of sedation, a better performance was observed with BIS in comparison to ANI (ROC curve AUC [95% CI]=0.91 [0.86-0.94] *vs*. 0.68 [0.61-0.74], respectively, P<0.05).

Conclusion. ANI exhibits good performance for the prediction of hemodynamic reactivity and BIS exhibits good performance for the assessment of sedation during suspension laryngoscopy with propofol/remifentanil total intravenous anesthesia. *(Minerva Anestesiol 2015;81:288-97)*

Key words: Analgesia - Anesthesia - Laryngoscopy.

Because of their short-acting pharmacodynamic properties, propofol and remifentanil are the agents of choice for sedation and analgesia in endoscopic procedures. Their administration during total intravenous anesthesia (TIVA) may be performed using manually controlled infusion, target-controlled infusion or patient-controlled administration, although the optimal method is still debated.[1-3] The objective of TIVA during suspension laryngoscopy is to provide adequate sedation and analgesia while maintaining spontaneous ventilation. A tight control of

Comment in p. 255

propofol and remifentanil dosing is necessary to avoid unwanted effects, such as apnoea in spontaneously breathing patients, reactions to painful stimuli and hemodynamic reactivity.[4]

According to the American Society of Anesthesiologists (ASA) guidelines, sedation and analgesia comprise a continuum of states ranging from minimal sedation (anxiolysis) to moderate sedation/analgesia (conscious sedation), deep sedation then general anesthesia.[5] Many studies have aimed to determine an objective measurement of sedation during endoscopic procedures. A clinical score, the Observer's Assessment of Alertness/Sedation (OAA/S) scale, may be used to measure the level of alertness in sedated subjects.[6, 7] Depth of sedation may also be assessed during endoscopic procedures using bispectral index (BIS) monitoring, a non-invasive measurement of electroencephalographic (EEG) activity ranging from 0 (deep anesthesia) to 100 (awake).[8]

Clinical signs, such as tachycardia and hypertension, usually assess nociception during general anesthesia. Several surrogate measures of depth of analgesia such as heart rate variability, skin conductance, surgical stress index or spectral entropy have been studied during surgery with various results.[9-15] To date, there are minimal data regarding analgesia monitoring during endoscopy.[16]

The Analgesia/Nociception Index (ANI), a non-invasive 0-100 index derived from heart rate variability reflecting the relative parasympathetic tone, has been recently reported to assess and predict immediate postoperative pain after surgery or suspension laryngoscopy.[17, 18] It has also been used to assess hemodynamic reactivity during propofol/remifentanil TIVA for laparoscopic surgery.[19] We hypothesized that ANI may not only assess but also predict hemodynamic reactivity related to nociception during suspension laryngoscopy performed with propofol/remifentanil TIVA. Our primary objective was to investigate the performance of ANI for the prediction of hemodynamic reactivity during this procedure. Our secondary objectives were to investigate the performances of both ANI and BIS for the assessment of sedation and of BIS for the prediction of hemodynamic reactivity.

Materials and methods

This prospective observational study was approved by the Institutional Review Board (Comité de Protection des Personnes Sud-Est III, study identifier CPP 2012-046B, ClinicalTrials.gov identifier NCT01796210) and performed between October 2012 and April 2013 at Édouard Herriot hospital, Lyon, France. The methodology followed the recommendations of STROBE statement.[20] After written informed consent was obtained, ASA physical status I–III patients undergoing suspension laryngoscopy using TIVA were included. Exclusion criteria were: age <18 years or >75 years, arrhythmia, preoperative use of β-blockers, preoperative chronic pain, autonomic nervous system disorders (epilepsy, history of stroke) and administration of anticholinergic drugs or vasopressors during the procedure.

Anesthetic technique

Hydroxyzine 50-100 mg and effervescent ranitidine were administered orally 1 h before induction of anesthesia. After arrival in the operating room, the patients were monitored with a three-lead electrocardiogram, pulse oxymetry recorded continuously and non-invasive blood pressure recorded every 5 min during the procedure (Philips IntelliVue MP20™, Philips Healthcare, Best, The Netherlands). A BIS Quatro™ sensor (Covidien, Mansfield, MA, USA) was applied to the forehead of each patient and BIS was measured using the A-2000™ XP monitoring system (Aspect Medical System Inc., Norwood, MA, USA).

After 3-min preoxygenation through facial mask, TIVA was induced using propofol 2 mg kg^{-1} followed by using a 6 mg kg^{-1} h^{-1} continuous infusion further adapted to maintain BIS values in the 40-60 range by 1 mg kg^{-1} h^{-1} steps at the discretion of the attending anesthesiologist.[21] Remifentanil was administered as a target-controlled infusion using the Minto model (Injectomat Agilia® pump, Fresenius Kabi AG, Bad Homburg, Germany) with an initial effect-site concentration (Ce) of 4 ng mL^{-1} until insertion of the suspension laryngo-

scope, then lowered to 2 ng mL^{-1}.[22] Throughout the procedure, signs of inadequate analgesia (tachycardia, hypertension or movement) were treated by increasing remifentanil by 0.5 to 1 ng mL^{-1} at the discretion of the attending anesthesiologist. Topical local anesthesia with 5% lidocaine was applied to the patient airway by the surgeon before the procedure. During the procedure, all patients breathed spontaneously and received continuous oxygen at a flow of 6 L min^{-1} through a nasal cannula. In case of apnoea lasting more than 2 min or desaturation (SpO_2 <90%), facemask ventilation was provided using a breathing system.

Multimodal analgesia was provided at the end of the procedure at the discretion of the attending anesthesiologist using intravenous paracetamol, ketoprofen, nefopam or tramadol in combination according to their respective contraindications.[23] Propofol and remifentanil were then discontinued, and 100% O_2 was given with 10 L min^{-1} fresh gas flow. When the patient was alert, with a respiratory rate >12 cycles min^{-1}, he was sent to post-anesthesia care unit (PACU).

Study protocol and ANI measurement

The anesthesia care provider was blinded to ANI monitoring. The ANI was obtained from each patient using the PhysioDoloris® monitor (MDoloris Medical Systems, Lille, France) connected to the patient monitor. This non-invasive device takes an ECG analogue output from the patient monitor and displays an average measurement of the ANI over the previous two minutes. Details on ANI calculation have been described elsewhere.[24-26] The ANI is an average score over two previous minutes but the calculation is performed every 4 s, which explains why ANI variations may be observed in 1-min intervals.[25] Briefly, the ANI is a 0-100 index derived from the high-frequency component of heart rate variability modulated by the influence of respiratory sinus arrhythmia on the RR series, reflecting the analgesia-nociception balance.[25] Higher ANI values indicate prominent parasympathetic tone, as observed during adequate analgesia.[10] In case of nociception, sympathetic tone increases and parasympathetic tone decreases, leading to decreased ANI values and hemodynamic reactivity.[10]

The ANI, BIS, hemodynamic and anesthetic data and level of consciousness were recorded during the procedure at predefined time points: T0 (before induction), T1 (1 min after the insertion of the suspension laryngoscope), T2 (during the procedure at steady-state anesthesia or in case of hemodynamic reactivity, corresponding to the 5 min preceding the reactivity) and T3 (at eye opening in the end of the procedure). In case of multiple episodes of hemodynamic reactivity during the procedure, only the first episode was considered. The level of consciousness was determined by using the OAA/S scale, ranging from 1, deep sedation (patient not responding to mild prodding or shaking) to 5, fully awake (patient responding readily to name spoken in normal tone).[6] Sedation during the procedure was defined as OAA/S≤2. Hemodynamic reactivity was defined as an increase by more than 20% of heart rate and/or systolic blood pressure within 5 min at the different time points. All anesthetic data including ANI measurements were recorded using DIANE® 4.4.5 software (Bow Médical, Amiens, France) for further analysis.

Statistical analysis

The primary outcome variable was the performance of ANI to predict hemodynamic reactivity, represented by the area under the receiver-operating curve (ROC curve AUC). Considering that an expected ROC curve AUC of 0.85 would be significantly different from the null hypothesis of 0.5 (meaning no discriminating power), a minimal number of 20 patients per group (positive and negative) was required with α=5% and 80% power. We enrolled a total number of 50 patients in this observational study. The secondary outcome variables were the performance of BIS to predict hemodynamic reactivity and of both ANI and BIS to assess sedation. Statistical analysis was performed using MedCalc® version 12.1.4.0 (MedCalc Software, Mariakerke, Belgium) and Statistica® version 8.0 (Stat Soft Inc., Tulsa, OK, USA). Changes in ANI and BIS values at study time points were assessed using one-way repeated-measures analysis of variance

(ANOVA) and Kruskal-Wallis test, respectively, after testing the normality of their distribution using Kolmogorov-Smirnov test. Student-Newman-Keuls test and Conover test were respectively used for *post hoc* ANI and BIS pairwise comparisons. The variations of heart rate and systolic blood pressure within 5 min were compared at each time-point and during the procedure using ANOVA for repeated measures with Bonferroni test for *post hoc* comparisons. The relationship between ANI and remifentanil Ce was determined using linear regression.

A receiver-operating characteristic (ROC) curve was built by plotting the sensitivity, or true positive rate, as a function of the false positive rate (100-specificity) of ANI at the different time points to detect the occurrence or the absence of hemodynamic reactivity. Other ROC curves were built to evaluate the performance of ANI for the assessment of sedation (OAA/S≤2) and of BIS for both the assessment of sedation and prediction of hemodynamic reactivity. Comparisons of ROC curves were performed using the method for the calculation of the standard error of the AUC and of the difference between two AUCs.[27] The software generated using Youden index the ANI and BIS values with the highest sensitivity and specificity for both the prediction of hemodynamic reactivity within 5 min and the assessment of sedation. Results were expressed as mean±SD, median (IQR) or N. (%). The threshold for statistical significance was set at $P<0.05$.

Results

Of the 96 patients undergoing suspension laryngoscopy during the study period, 22 missed the invitation to participate or declined to be invited, leaving 74 patients assessed for eligibility (Figure 1). Of these patients, 20 were excluded and among the 54 patients included, 4 were

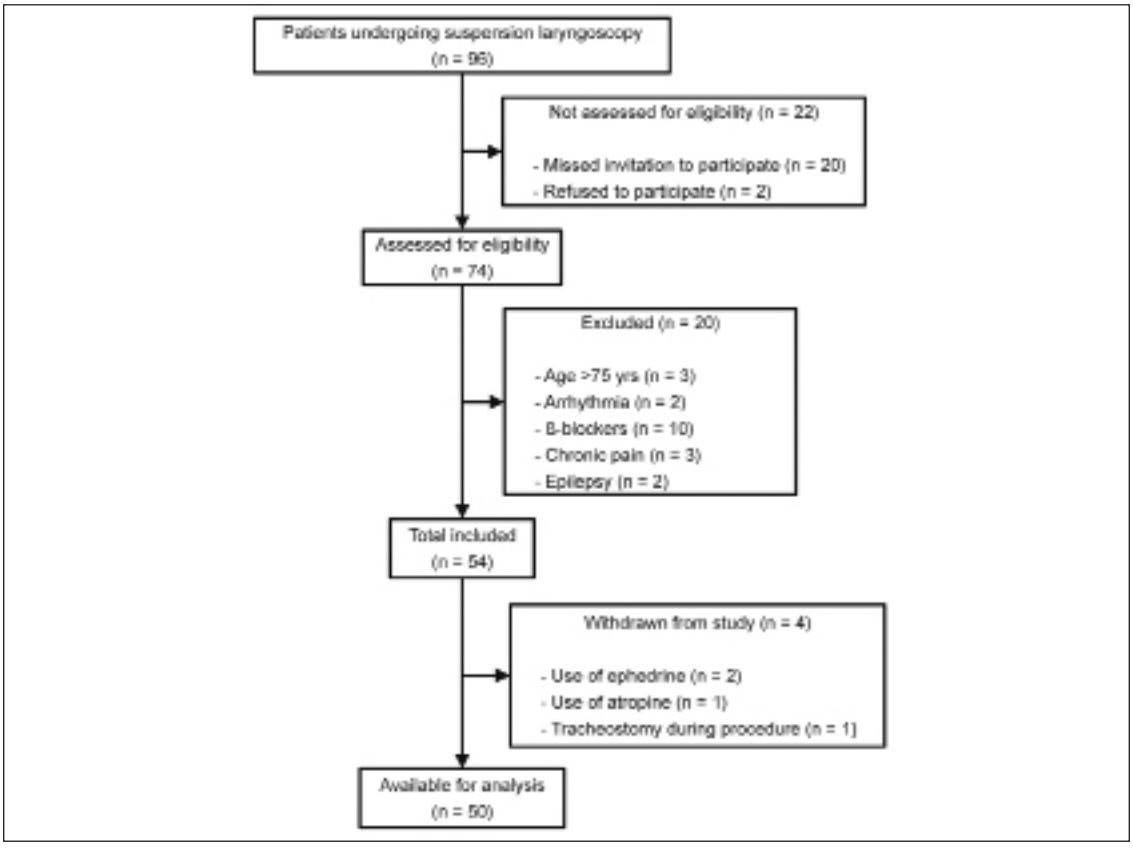

Figure 1.—Flow chart.

Table I.—*Intrinsic and extrinsic performances of ANI and BIS to predict hemodynamic reactivity (increase of heart rate and/or systolic blood pressure by more than 20% from baseline within 5 min) and to assess sedation (OAA/S≤2) during propofol/remifentanil suspension laryngoscopy.*

N.=200 (pooled data)	Se	Sp	PPV	NPV
Prediction of haemodynamic reactivity*				
ANI≤55	88 (76-96)	83 (76-89)	64 (52-76)	95 (90-98)
BIS≤79	90 (79-97)	47 (39-55)	37 (28-46)	93 (85-98)
Assessment of sedation*				
ANI≤58	60 (47-72)	69 (61-77)	49 (38-61)	77 (69-85)
BIS≤63	88 (78-95)	85 (78-91)	75 (64-84)	93 (87-97)

*Thresholds determined using Youden index. ANI: Analgesia/Nociception Index; BIS: Bispectral Index; OAA/S: observer's assessment of alertness/sedation; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value. Values in parentheses are 95% confidence interval.

withdrawn from the study, leaving 50 patients for analysis (Figure 1). Characteristics of all 50 evaluable patients and indications for suspension laryngoscopy are shown in Table I. A total of 200 simultaneous observations (ANI, BIS, OAA/S and hemodynamic reactivity) were recorded in

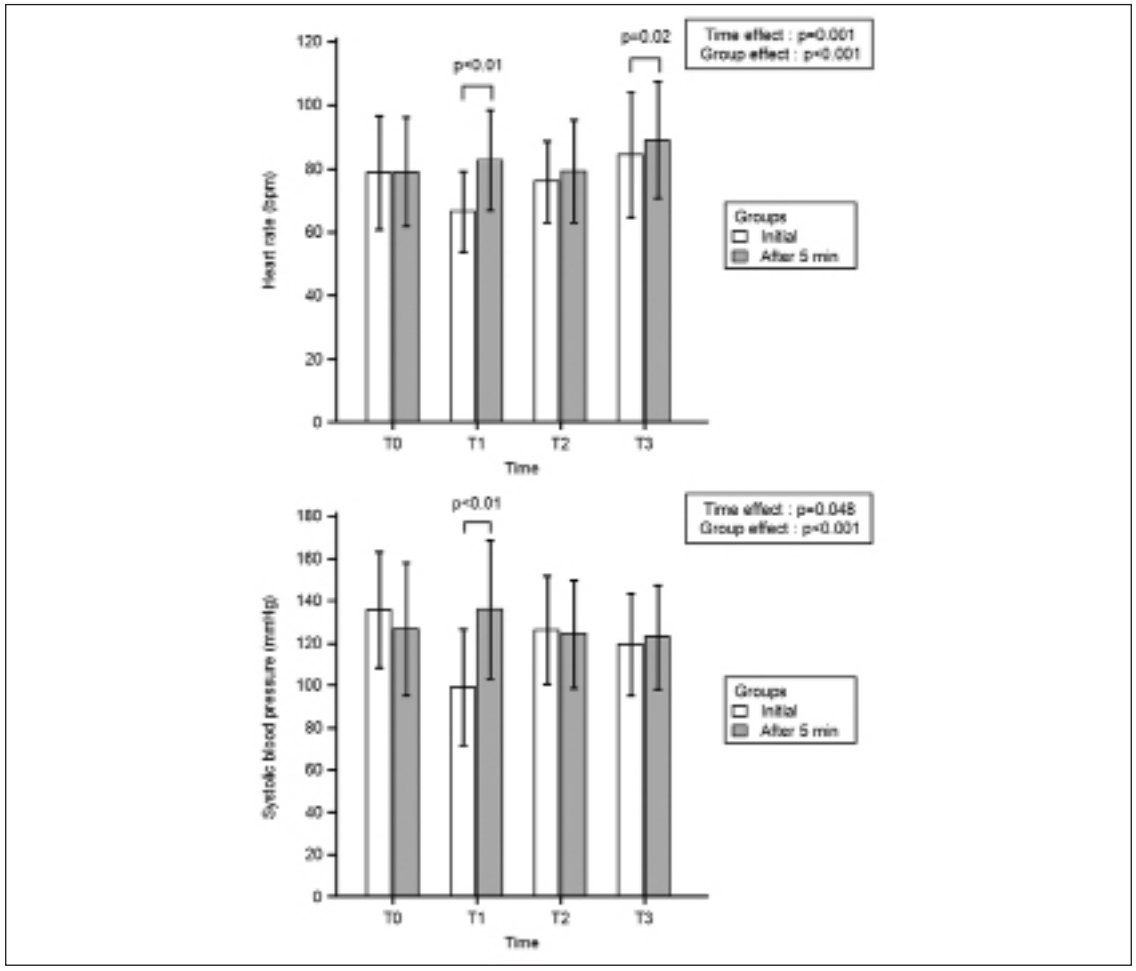

Figure 2.—Mean variations of heart rate (upper panel) and systolic blood pressure (lower panel) at the different time-points during the procedure. The errors bars represent standard deviations. T0=before induction; T1=1 min after insertion of suspension laryngoscope; T2=during the procedure at steady-state anesthesia or 5 min before an episode of hemodynamic reactivity; and T3=at eye opening in the end of the procedure.

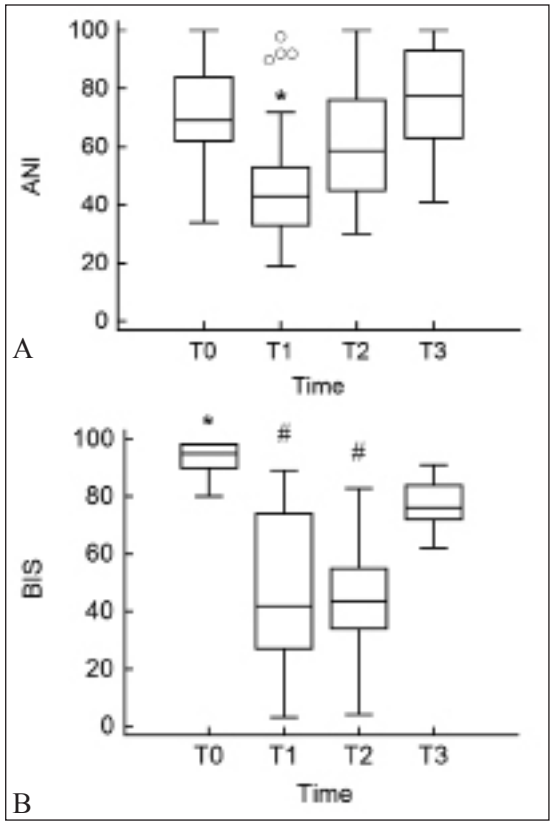

Figure 3.—Variations of ANI (A) and BIS (B) at the different time points during the procedure. The box-and-whisker plot represents medians (center line), quartiles (box), range (bars) and outliers (circles). T0=before induction; T1=1 min after insertion of suspension laryngoscope; T2=during the procedure at steady-state anesthesia or 5 min before an episode of hemodynamic reactivity; and T3=at eye opening in the end of the procedure. *P<0.05 *vs*. other time groups. #P<0.05 *vs*. T0 and T3.

these patients. Variations of heart rate and systolic blood pressure at the different time intervals are presented in Figure 2. Seven patients (14 %) required facemask ventilation during 1-2 min for 1 or 2 episodes of desaturation rapidly reversible without complications (Table II). Measurements were correctly performed in all patients without any missing values.

The mean±SD ANI values were significantly lower (P<0.01) at T1 (46±18) in comparison to T0, T2 and T3 (72±14, 61±20 and 75±17, respectively) (Figure 3). The median (IQR) BIS values were significantly higher at T0 (95 [90-98]) in comparison to other time groups and significantly lower at T1 (42 [27-74]) and T2 (44 [34-55]) in comparison to T0 and T3 (76 [72-84]) (Figure 3). There was a small, although significant, negative linear relationship between ANI and remifentanil Ce (ANI=-7.6 x Ce + 74.7, r=-0.44, P<0.001).

Table II.—*Patient characteristics (N.=50).*

Age (yrs)	53±17
Gender	
Male	36 (72)
Female	14 (28)
ASA physical status	
I	14 (28)
II	26 (52)
III	10 (20)
Body mass index (kg/m^2)	25±4
Total dose of propofol (mg)	385±170
Total dose of remifentanil (μg)	271±145
Indication for suspension laryngoscopy	
Suspicion of laryngeal cancer	20 (40)
Vocal cord polyp	14 (28)
Laryngeal papillomatosis	15 (30)
Vocal cord paralysis	1 (2)
Respiratory rate (cycles/min)	
T0 (before induction)	14±3
T1 (1 min after laryngoscopy)	15±5
T2 (during procedure)	13±4
T3 (at eye opening)	15±3
Facemask ventilation during procedure	7 (14)
Duration of procedure (min)	20±10

Results are mean±SD or N. (%).

The ROC curves plotted with pooled data of all time points determining the performances of ANI and BIS for the prediction of hemodynamic reactivity are shown in Figure 4A, showing better performance for ANI in comparison to BIS (ROC curve AUC [95% CI] = 0.88 [0.83-0.92] *vs*. 0.73 [0.66-0.79], respectively, P<0.05). The ROC curves determining the performances of ANI and BIS for the assessment of sedation (OAA/S≤2) are shown in Figure 4B, showing better performance for BIS in comparison to ANI (ROC curve AUC [95% CI] = 0.91 [0.86-0.94] *vs.* 0.68 [0.61-0.74], respectively, P<0.05). The intrinsic (sensitivity and specificity) and extrinsic (positive and negative predictive values) performances of ANI and BIS to predict hemodynamic reactivity and to assess sedation are reported in Table I. At the threshold of ≤55, the sensitivity and specificity of ANI to predict hemodynamic reactivity within 5 min were 88% and 83%, respectively, with 64% positive predictive value and 95% negative predictive value.

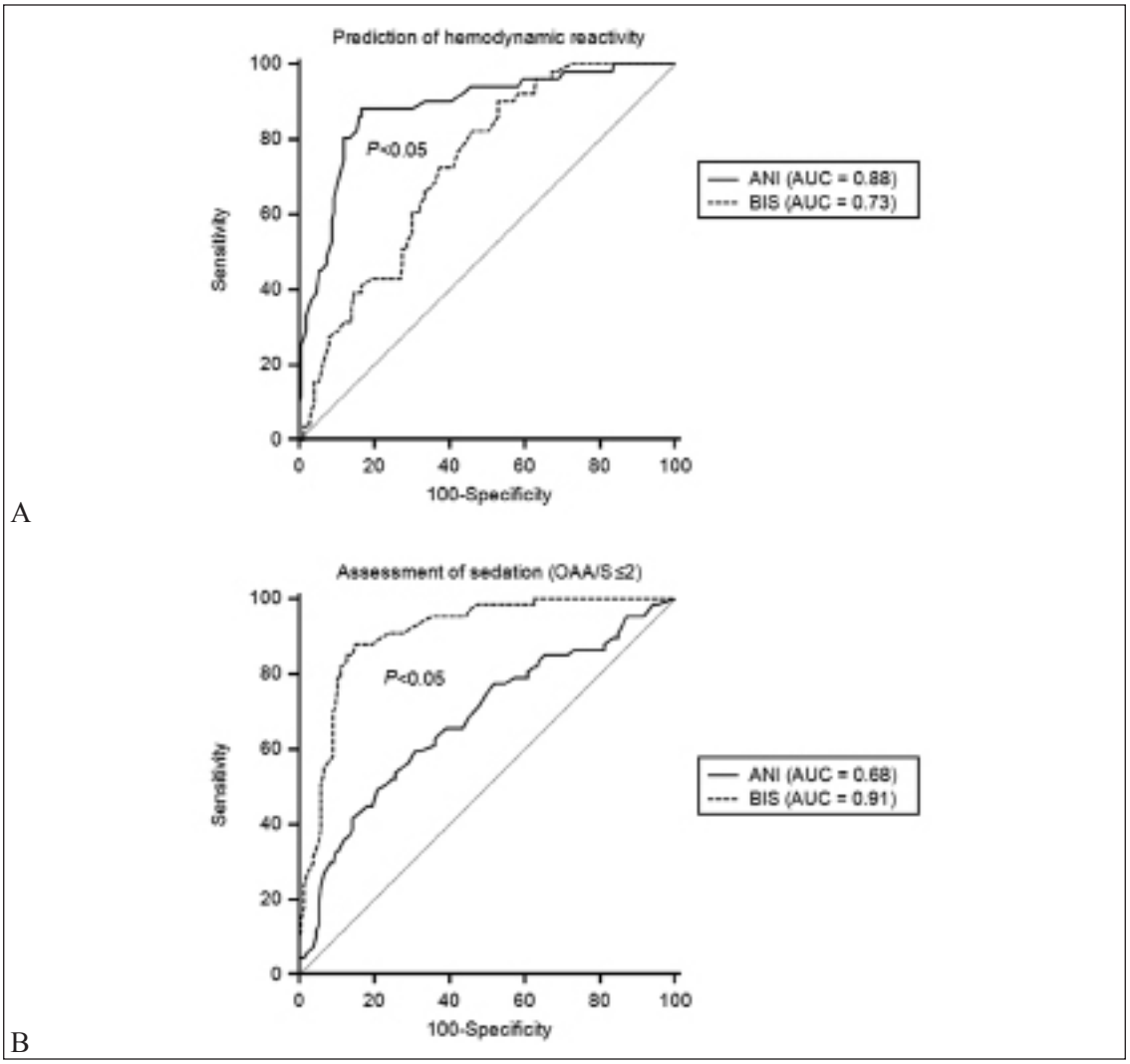

Figure 4.—Comparative ROC curves (pooled data) of ANI and BIS for the prediction of hemodynamic reactivity (A) and for the assessment of sedation (B).

Discussion

This study demonstrates that during suspension laryngoscopy using propofol/remifentanil TIVA, ANI exhibits good performance for the prediction of hemodynamic reactivity (ROC curve AUC>0.8) but not for the assessment of sedation (ROC AUC<0.8).[28] On the contrary, BIS exhibits good performance for the assessment of sedation as previously reported [7, 29] but not for the prediction of hemodynamic reactivity. This suggests that ANI may be a reliable indicator of nociception during endoscopic procedures and may therefore constitute a useful analgesia monitor in addition to BIS monitoring.

The measurement of depth of anesthesia is clinically relevant for the titration of anesthetic agents and for avoiding patient awareness during procedural sedation.[7, 8] The hypnotic component of anesthesia has been monitored during endoscopic procedures in previous studies using BIS.[7, 21, 29, 30] It has however been reported that BIS or other anesthetic depth measurements should not be used without considering the relative contributions of hypnotic and opioid agents to the anesthetics state.[31] Pharmacodynamic

interactions between propofol and remifentanil have been reported, showing potent synergy to blunt hemodynamic responses to laryngoscopy, intubation or surgical stimulation and for the return to consciousness.[31, 32] Propofol and remifentanil modulate frontal electroencephalic activity differently, with BIS being more sensitive to the hypnotic component (propofol) than to the analgesic component (remifentanil) of anesthesia.[31, 33, 34] When coadministered with propofol, remifentanil seems to suppress the propofol-induced electroencephalographic changes and create some of its own, hindering the interpretation of the EEG-based depth of anesthesia indexes.[35]

However, there are only few data regarding the monitoring of the analgesic component of anesthesia during endoscopic procedures. The question of analgesia monitoring is still unsolved since indirect and non-specific clinical signs are used for pain assessment during anesthesia, such as tachycardia, hypertension or movement.[9] The utility of a beat-by-beat cardiovascular index for the reduction of movement during colonoscopy has been reported.[16] The measurement consisted of a beat-by-beat finger blood pressure monitor combined with an algorithm detecting hypertension followed by tachycardia related to increased sympathetic activity, producing an index named CARDEAN ranging from 0 to 100. In this study, patients undergoing colonoscopy with TIVA received propofol adjusted to maintain BIS values between 40 and 60 and alfentanil 3.5 μg/kg administered according to conventional signs of pain (tachycardia, hypertension, and movement) or if CARDEAN was ≥60 in addition to conventional signs. The authors observed a significant reduction of movement in patients with CARDEAN-guided alfentanil administration. However, the performance of CARDEAN to predict movement was somewhat poor (ROC curve AUC of 0.68) with 30% sensitivity and 86% specificity at the threshold of 60.

In the current study, the clinical sign used for pain assessment during the procedure was not movement but hemodynamic reactivity. Indeed, the lack of motor response may not accurately predict the ability of an agent to blunt hemodynamic reactions, whether tachycardia and/or hypertension following noxious stimulation such as laryngoscopy are still considered as responses easy to interpret during anesthesia.[9, 36] Hemodynamic reactivity following nociception may serve to manually adapt the dosage of anesthetic agents. Automatic administration of remifentanil based on variations of heart rate, mean arterial blood pressure and heart rate variability has been recently used combined with a closed-loop propofol infusion system for hypnosis.[37] Closed-loop systems have also been used for the titration of propofol target-control infusion guided by BIS monitoring during induction and maintenance of general anesthesia.[38] Moreover, the automated dual-loop coadministration of propofol and remifentanil guided by the electroencephalogram differential analysis of hypnosis and analgesia has been shown to be more reliable than manual administration during elective surgery.[39] However, in this study, the authors stated that determining whether remifentanil administration was adequate with the closed-loop controller was challenging since there was no specific measure of intraoperative analgesia. One may therefore hypothesize that ANI could further be used for analgesia monitoring in combination to BIS or any other hypnosis monitoring to integrate both the analgesic and hypnotic components of depth of anesthesia in the manual or dual automated administration of remifentanil and propofol during TIVA, although this remains to be demonstrated.

Our study presents however some limitations. First, many patients were excluded (*e.g.* patients with arrhythmia or using medications known to alter heart rate variability such as β-adrenoreceptor antagonists) which may limit ANI monitoring in these populations. Second, patients receiving atropine or ephedrine during the procedure were withdrawn from the study. The use of these drugs is frequent during general anesthesia and to date, no data is available to determine whether cardiovascular drugs modify the ANI predictability of hemodynamic reactivity; therefore our results may not be extrapolable to all patients requiring TIVA for suspension laryngoscopy. Third, the ANI calculation is based on the modulation of the RR series by respiratory sinus arrhythmia leading to a ventilatory pattern appearing at regular intervals.[26] Therefore,

ANI is not recorded during apnoea, which may occur during suspension laryngoscopy, and its use may be limited in the following minutes. Last, our study was observational and designed for determining ANI thresholds predictive of hemodynamic reactivity. Besides, propofol and remifentanil dosing was left at the discretion of the attending anesthesiologist, which might have introduced bias in the analysis of the predictive ability of ANI. Further study comparing ANI-monitored patients versus traditional clinical signs is needed to determine the benefit of ANI during routine anesthesia, in particular for optimizing remifentanil administration in order to avoid hemodynamic reactivity or episodes of apnoea.

Conclusions

In conclusion, ANI monitoring exhibits good performance for the prediction of hemodynamic reactivity (ROC curve AUC = 0.88) in patients undergoing suspension laryngoscopy under propofol/remifentanil TIVA, with 88% sensitivity and 83% specificity at the threshold of ≤55. In our study population, ANI exhibited better performance than BIS for the prediction of hemodynamic reactivity, whereas BIS exhibited better performance than ANI for the assessment of sedation. Considering that anesthesia is composed of both sedation and analgesia, ANI may be useful for monitoring depth of analgesia in conjunction with clinical signs such as OAA/S or BIS for monitoring depth of sedation during suspension laryngoscopy using propofol/remifentanil TIVA. Further studies are needed to determine the benefit of ANI monitoring during routine clinical practice.

Key messages

— The objective of anesthesia during suspension laryngoscopy is to provide adequate sedation and analgesia while maintaining spontaneous ventilation.

— The Analgesia/Nociception Index (ANI) is a 0-100 index derived from heart rate variability reflecting the relative parasympathetic tone.

— During suspension laryngoscopy using total intravenous anesthesia (TIVA) with propofol and remifentanil, ANI exhibited good performance for the prediction of hemodynamic reactivity (ROC curve AUC [95% CI] = 0.88 [0.83-0.92]), with 88% sensitivity and 83% specificity for ANI ≤55.

— ANI may be useful for monitoring depth of analgesia in conjunction with bispectral index (BIS) for monitoring depth of sedation during suspension laryngoscopy on propofol/remifentanil TIVA.

References

1. Bouvet L, Allaouchiche B, Duflo F, Debon R, Chassard D, Boselli E. Le rémifentanil est une alternative efficace au propofol pour l'analgésie auto-contrôlée en endoscopie digestive. Can J Anesth 2004;51:122-5.
2. Leslie K, Clavisi O, Hargrove J. Target-controlled infusion versus manually-controlled infusion of propofol for general anesthesia or sedation in adults. Cochrane Database Syst Rev 2008:CD006059.
3. Moerman AT, Herregods LL, De Vos MM, Mortier EP, Struys MM. Manual versus target-controlled infusion remifentanil administration in spontaneously breathing patients. Anesth Analg 2009;108:828-34.
4. Passot S, Servin F, Allary R, Pascal J, Prades JM, Auboyer C *et al*. Target-controlled versus manually-controlled infusion of propofol for direct laryngoscopy and bronchoscopy. Anesth Analg 2002;94:1212-6.
5. American Society of Anesthesiologists Task Force on S, Analgesia by N-A. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96:1004-17.
6. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB *et al*. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol 1990;10:244-51.
7. Bower AL, Ripepi A, Dilger J, Boparai N, Brody FJ, Ponsky JL. Bispectral index monitoring of sedation during endoscopy. Gastrointest Endosc 2000;52:192-6.
8. Myles PS, Leslie K, McNeil J, Forbes A, Chan MT. Bispectral index monitoring to prevent awareness during anesthesia: the B-Aware randomised controlled trial. Lancet 2004;363:1757-63.
9. Guignard B. Monitoring analgesia. Best Pract Res Clin Anesthesiol 2006;20:161-80.
10. Jeanne M, Logier R, De Jonckheere J, Tavernier B. Heart rate variability during total intravenous anesthesia: effects of nociception and analgesia. Auton Neurosci 2009;147:91-6.
11. Ledowski T, Pascoe E, Ang B, Schmarbeck T, Clarke MW, Fuller C *et al*. Monitoring of intra-operative nociception: skin conductance and surgical stress index versus stress hormone plasma levels. Anesthesia 2010;65:1001-6.
12. Chen X, Thee C, Gruenewald M, Wnent J, Illies C, Hoecker J *et al*. Comparison of surgical stress index-guided analgesia with standard clinical practice during routine general anesthesia: a pilot study. Anesthesiology 2010;112:1175-83.

13. Takamatsu I, Ozaki M, Kazama T. Entropy indices vs the bispectral index for estimating nociception during sevoflurane anesthesia. Br J Anesth 2006;96:620-6.
14. von Dincklage F, Correll C, Schneider MH, Rehberg B, Baars JH. Utility of Nociceptive Flexion Reflex Threshold, Bispectral Index, Composite Variability Index and Noxious Stimulation Response Index as measures for nociception during general anesthesia. Anesthesia 2012;67:899-905.
15. Gruenewald M, Ilies C. Monitoring the nociception-anti-nociception balance. Best Pract Res Clin Anesthesiol 2013;27:235-47.
16. Martinez JY, Wey PF, Lions C, Cividjian A, Rabilloud M, Bissery A *et al*. A beat-by-beat cardiovascular index, CARDEAN: a prospective randomized assessment of its utility for the reduction of movement during colonoscopy. Anesth Analg 2010;110:765-72.
17. Boselli E, Daniela-Ionescu M, Bégou G, Bouvet L, Dabouz R, Magnin C *et al*. Prospective observational study of the non-invasive assessment of immediate postoperative pain using the analgesia/nociception index (ANI). Br J Anesth 2013;111:453-9.
18. Boselli E, Bouvet L, Bégou G, Dabouz R, Davidson J, Deloste JY *et al*. Prediction of immediate postoperative pain using the analgesia/nociception index: a prospective observational study. Br J Anesth 2014;112:715-21.
19. Jeanne M, Clement C, De Jonckheere J, Logier R, Tavernier B. Variations of the analgesia nociception index during general anesthesia for laparoscopic abdominal surgery. J Clin Monit Comput 2012;26:289-94.
20. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ *et al*. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med 2007;4:e297.
21. Bould MD, Mahtani DG, Davies R, Roughton M, Hunter DN, Kelleher A. Bispectral index values during elective rigid bronchoscopy: a prospective observational pilot study. Anesthesia 2007;62:438-45.
22. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL *et al*. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 1997;86:10-23.
23. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248-73.
24. Jeanne M, Logier R, De Jonckheere J, Tavernier B. Validation of a graphic measurement of heart rate variability to assess analgesia/nociception balance during general anesthesia. Conf Proc IEEE Eng Med Biol Soc 2009;2009:1840-3.
25. Logier R, Jeanne M, De Jonckheere J, Dassonneville A, Delecroix M, Tavernier B. PhysioDoloris: a monitoring device for analgesia / nociception balance evaluation using heart rate variability analysis. Conf Proc IEEE Eng Med Biol Soc 2010;2010:1194-7.
26. Logier R, Jeanne M, Tavernier B, De Jonckheere J. Pain/analgesia evaluation using heart rate variability analysis. Conf Proc IEEE Eng Med Biol Soc 2006;1:4303-6.
27. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-45.
28. Galley HF. Editorial II: Solid as a ROC. Br J Anesth 2004;93:623-6.
29. von Delius S, Thies P, Rieder T, Wagenpfeil S, Herberich E, Karagianni A *et al*. Auditory evoked potentials compared with bispectral index for monitoring of midazolam and propofol sedation during colonoscopy. Am J Gastroenterol 2009;104:318-25.
30. Paspatis GA, Chainaki I, Manolaraki MM, Vardas E, Theodoropoulou A, Tribonias G *et al*. Efficacy of bispectral index monitoring as an adjunct to propofol deep sedation for ERCP: a randomized controlled trial. Endoscopy 2009;41:1046-51.
31. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C *et al*. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology 2004;100:1353-72.
32. Mertens MJ, Olofsen E, Engbers FH, Burm AG, Bovill JG, Vuyk J. Propofol reduces perioperative remifentanil requirements in a synergistic manner: response surface modeling of perioperative remifentanil-propofol interactions. Anesthesiology 2003;99:347-59.
33. Liley DT, Sinclair NC, Lipping T, Heyse B, Vereecke HE, Struys MM. Propofol and remifentanil differentially modulate frontal electroencephalographic activity. Anesthesiology 2010;113:292-304.
34. Koitabashi T, Johansen JW, Sebel PS. Remifentanil dose/electroencephalogram bispectral response during combined propofol/regional anesthesia. Anesth Analg 2002;94:1530-3.
35. Kortelainen J, Koskinen M, Mustola S, Seppänen T. Effects of remifentanil on the spectrum and quantitative parameters of electroencephalogram in propofol anesthesia. Anesthesiology 2009;111:574-83.
36. Zbinden AM, Petersen-Felix S, Thomson DA. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. II. Hemodynamic responses. Anesthesiology 1994;80:261-7.
37. Janda M, Schubert A, Bajorat J, Hofmockel R, Noldge-Schomburg GF, Lampe BP *et al*. Design and implementation of a control system reflecting the level of analgesia during general anesthesia. Biomed Tech (Berl) 2013;58:1-11.
38. Liu N, Chazot T, Genty A, Landais A, Restoux A, McGee K *et al*. Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: closed-loop versus manual control: a prospective, randomized, multicenter study. Anesthesiology 2006;104:686-95.
39. Liu N, Le Guen M, Benabbes-Lambert F, Chazot T, Trillat B, Sessler DI *et al*. Feasibility of closed-loop titration of propofol and remifentanil guided by the spectral M-Entropy monitor. Anesthesiology 2012;116:286-95.

Funding.—This work was supported by the Department of Anesthesiology, Édouard Herriot Hospital, Lyon, France.
Conflicts of interest.—E. Boselli has received a travel grant for MDoloris Medical Systems for a conference presentation.
Preliminary data for this study were presented as a poster presentation at the French Society of Anaesthesia and Intensive Care Medicine (SFAR) annual meeting, 18-21 September 2013, Paris, France.

Received on April 8, 2014. - Accepted for publication on July 8, 2014. - Epub ahead of print on July 11, 2014.

Corresponding author: E. Boselli, MD, Hôpital Édouard Herriot, Service d'anesthésie-réanimation, 5 place d'Arsonval, 69003 Lyon, France. E-mail: emmanuel.boselli@chu-lyon.fr