Prediction of Movement to Surgical Stimulation by the Pupillary Dilatation Reflex Amplitude Evoked by a Standardized Noxious Test

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ABSTRACT

Background: Individual assessment of the amplitude of a physiologic reflex evoked by a standardized noxious test (SNT) before surgical stimulation has been suggested to predict movement upon the forthcoming surgical stimulation. This study aimed to compare the ability of pupillary dilatation reflex amplitude (PDRA) evoked by an SNT and estimated remifentanil effect-site concentration (Ce) to predict movement upon surgical stimulation.

Methods: Eighty female patients were anesthetized for vacuum aspiration with propofol (Ce 4 μg/ml) and remifentanil. Remifentanil Ce was randomized to 0, 1, 3, or 5 ng/ml. SNT was a 60-mA, 5-s, 100-Hz tetanus applied on median nerve before cervix dilatation. PDRA was calculated as the difference in pupillary diameter after and before SNT. Movement upon cervix dilatation was recorded by an independent observer. Ability of PDRA and estimated remifentanil Ce to discriminate movers from non-movers during cervix dilatation was measured as the area under the receiver operating characteristics curve.

Results: Twenty-one of the 76 patients analyzed moved during cervix dilatation. Mean PDRA (±1 SD) evoked by SNT was 2.0 ± 1.2 mm in movers and 0.6 ± 0.7 in non-movers ($P < 0.0001$). Remifentanil Ce was 0.2 ± 0.4 ng/ml in movers and 3.0 ± 1.7 in non-movers ($P < 0.0001$). Area under the receiver operating characteristics curve for PDRA was 0.90 (95% CI, 0.83 to 0.96) and for remifentanil Ce 0.94 (0.89 to 0.98), without any significant difference between the two areas.

Conclusions: PDRA evoked by an SNT is as accurate as the estimated remifentanil Ce to predict movement upon cervix dilatation. PDRA could be valuable when estimated opioid Ce is not available or reliable. **(ANESTHESIOLOGY 2015; 122:985-93)**

THE most scientifically grounded approach to predict movement or hemodynamic response to noxious stimulations during surgery under total general anesthesia relies on pharmacokinetic–pharmacodynamic models for opioids and hypnotics.[1–3] These models take into consideration the synergistic interactions between opioids and hypnotics and give a population-based statistical prediction of response to a given stimulus.

An alternative approach to predict movement or hemodynamic response to noxious stimulations is based on the individual assessment of the amplitude of a physiologic reflex evoked by a standardized noxious test (SNT).[4,5] The amplitude is defined as the difference between the measured variable after application of the SNT and the measured variable before the SNT. For instance, Shimoda *et al.*[4] demonstrated that the amplitude of the skin vasomotor reflex evoked by an electrical SNT was correlated to the hemodynamic response to laryngoscopy in patients anesthetized with sevoflurane, nitrous oxide, and fentanyl. Similarly, Rehberg *et al.*[5] reported that the amplitude of the Hoffmann or H reflex elicited by an electrical SNT was correlated to the occurrence

What We Already Know about This Topic

- The likelihood of response to noxious stimulation during surgery under total intravenous anesthesia can be predicted using pharmacokinetic–pharmacodynamic models
- Alternatively, the balance between nociception and antinociception can be assessed in anesthetized patients by determining the amplitude of a physiologic reflex evoked by a standardized noxious test

What This Article Tells Us That Is New

- Seventy-six women scheduled for an operative procedure requiring cervical dilation were anesthetized with a target propofol effect-site concentration of 4 μg/ml with a randomly assigned remifentanil effect site concentration of 0, 1, 3, or 5 ng/ml
- Pupillary dilatation reflex amplitude in response to a standardized noxious test predicted movement response upon cervical dilation as accurately as the estimated remifentanil effect site concentration

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of movement in patients anesthetized with sevoflurane. The complexity of the measurements of these reflexes has so far precluded their use in daily clinical practice.

In anesthetized patients, a noxious stimulus evokes a pupillary dilatation reflex, mediated by an inhibition of the parasympathetic system.[6] Use of the amplitude of the pupillary dilatation reflex evoked by an SNT to individually assess the nociception/antinociception balance involves that reflex amplitude changes in a predictable way both when applying an experimental nociceptive stimulus and when administering opioids. These two requirements are fulfilled for the pupillary dilatation reflex. First, a linear relationship is observed between pupillary dilatation reflex amplitude (PDRA) and the intensity of the electrical current used during the SNT.[7,8] Second, a predictable relationship is observed between PDRA and opioid concentration. Larson *et al.*[9] reported a decreasing exponential relationship between PDRA and measured plasma alfentanil concentration. Barvais *et al.*[10] described a linear decreasing relationship between PDRA and estimated effect-site remifentanil concentration.[9] The pupillary dilatation reflex evoked by an SNT is now easily recorded with portable videopupillometers.[11,12] One may therefore hypothesize that PDRA evoked by an SNT before surgical stimulation in anesthetized patients may predict movement upon the forthcoming surgical stimulation.

The primary aim of this study was therefore to compare the ability of PDRA evoked by an SNT before surgical stimulation and estimated remifentanil effect-site concentration (Ce) to predict movement upon subsequent surgical stimulation. The secondary aim was to estimate PDRAs associated with 50 and 95% probabilities of nonmovement upon surgical stimulation

Materials and Methods

The study was approved by the Institutional Review Board of Hotel-Dieu Hospital ("Comité de Protection des Personnes, Ile-de-France 1"), Assistance Publique-Hôpitaux de Paris, Paris, France. Written informed consent was obtained from each patient. The study was conducted in Bichat-Claude Bernard Hospital, Paris.

Patients

Inclusion criteria were women undergoing planned vacuum aspiration for abortion or miscarriage under general anesthesia. Noninclusion criteria were as follows: age less than 18 yr, American Society of Anesthesiologists physical status greater than 2, requirement for endotracheal intubation, regular medication with β-blocker, anxiolytic, antidepressant or opioid, alcohol or drug abuse, body mass index greater than 30 kg/m^2, history of eye disease or eye surgery, diabetes, and hypertension.

Study Design

Patients were asked to participate in the study on the morning of surgery when they arrived in the outpatient clinic. They were recruited when two of the three investigators were available (J.G., N.G., M.P.). Once included, patients were randomized to one of the four following groups of remifentanil Ce: 0, 1, 3, or 5 ng/ml. Randomization used a computer-generated random number sequence in blocks of eight patients, and group allocation used sealed opaque envelopes. The envelope was opened in the operating room by the attending anesthesiologist. A summary of the experimental timeline is presented in figure 1.

Definition of Outcome and Predictors

The outcome was the occurrence of movement upon surgical stimulation (*i.e.*, cervix dilatation). Movement was defined as a purposeful movement of the left upper limb, movement of the lower limbs, cough, or laryngospasm. It was recorded by an investigator blinded to both remifentanil Ce and pupillary assessment results.

The variables considered as potential predictors of movement upon surgical stimulation were assessed by an investigator blinded to remifentanil Ce. They were as follows:

- PDRA defined as the difference between the highest pupillary diameter (PD) recorded during the 10-s period after the SNT and PD before the SNT.
- Heart rate (HR), systolic blood pressure (SBP), and bispectral index (BIS) amplitudes defined as the difference between the highest value among three values recorded after SNT and the mean of three values recorded before SNT.
- Predicted remifentanil Ce with Minto model.[13,14]

Anesthesia Protocol

Patients undergoing abortion received 400-μg sublingual misoprostol on the morning of surgery according to hospital practice guidelines. No anxiolytic medication was given.

On arrival in the operating room, a 20-gauge intravenous catheter was inserted on the left upper limb. A triple lumen extension tube (Octopus3®; Vygon, France) was directly connected to the catheter with one lumen devoted to propofol infusion and one lumen devoted to remifentanil infusion. Patients were monitored with intermittent noninvasive blood pressure, 5-lead electrocardiogram, pulse oximetry, and BIS (BIS Vista®; Covidien, USA) on the right forehead. The smoothing interval for BIS analysis was 15 s. Three measurements of baseline HR, SBP, and BIS performed 30 s apart were recorded.

Anesthesia was induced and maintained with effect-site target-controlled infusions of propofol (Schnider model) and remifentanil (Minto model) administered with the Base Primea® infusion device (Fresenius-KABI, France).[13–15] The attending anesthesiologist who opened the sealed envelope programmed the infusion pump. Intravenous lidocaine to decrease pain caused by propofol infusion was not allowed. Propofol infusion (10 mg/ml) was started at a Ce of 4 μg/ml.[16] Remifentanil infusion (20 μg/ml) was simultaneously started at the randomized Ce. Remifentanil Ce was unchanged until surgical stimulation. If loss of consciousness (LOC) defined by loss of the eyelash reflex was not obtained when target Ce for both remifentanil and propofol were attained, the attending anesthesiologist could increase propofol Ce by 1 μg/ml

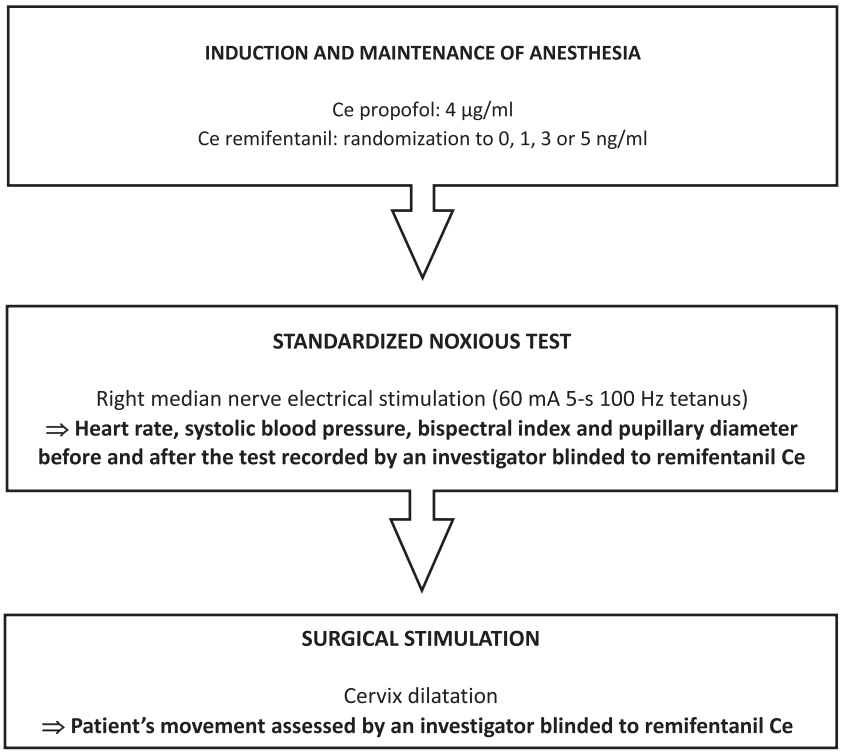

Fig. 1. Summary of the experimental timeline. Ce = effect-site concentration.

increments until LOC occurred. Once LOC was obtained, propofol Ce was unchanged until surgical stimulation. During anesthesia, manual face-mask ventilation was used with 100% oxygen. No administration of drugs known to alter pupil size or reactivity such as atropine or droperidol was allowed before SNT and surgical stimulation.

At least 2 min after target propofol and remifentanil Ce had been achieved, three measurements of HR, SBP, and BIS were performed 30 s apart followed by application of SNT on the right median nerve. The three measurements of HR, SBP, and BIS were repeated over a 90-s time period after the SNT, 30 s apart. The time period of 90 s was selected based on previous studies that demonstrated that the peak response of HR, an HR variability-derived index ("Analgesia Nociception Index"), and an electroencephalographic-derived index ("Composite Variability Index") to an electrical 50-Hz, 30-s, 50- to 70-mA stimulation of the ulnar nerve under propofol–remifentanil anesthesia occurred within 90 s of the stimulation.[17–19]

During surgical stimulation defined as the dilatation of the cervix, the occurrence of movement was recorded. In case of movement, surgical stimulation was stopped.

Standardized Noxious Test and Measurement of PD

PD was measured with an infrared portable dynamic videopupillometer (AlgiScan®, IDMed Company, France). The sampling frequency was 67 Hertz (*i.e.*, a PD recorded every 15 ms) and precision 0.05 mm.[11] The pupillometer was combined with an electrical stimulator.

The noxious stimulation consisted of a 60-mA, 5-s, 100-Hz tetanus applied on the right median nerve through two skin electrodes. It was applied at least 2 min after target Ce for both propofol and remifentanil were obtained. PD was recorded during 10 s after the end of the tetanus.

To avoid the influence of ambient lighting on PD, the pupillometer included a preformed silicone membrane surrounding the orbit under investigation. The contralateral eye was closed with an adhesive tape. Artifact during pupil scan was detected by visual inspection of the recording. A scan with artifacts was discarded, and the scan was repeated at least 1 min after the discarded one.

Statistical Analysis

Results are expressed as means (± 1SD) or numbers (%). When indicated, 95% confidence interval (CI) was calculated. The statistical analysis was performed with R version 3.0.2 (R Foundation for Statistical Computing, Austria).

The size of this study was based on a convenience sample of 20 patients in each group of remifentanil Ce. Comparisons across the four groups of remifentanil Ce used ANOVAs or chi-square tests. Comparisons of HR, SBP, BIS, and PD before and after SNT used paired Wilcoxon tests. Comparisons of HR amplitude, SBP amplitude, BIS amplitude, and PDRA evoked by SNT and remifentanil Ce between movers and non-movers upon surgical stimulation used unpaired Wilcoxon tests. The ability of HR amplitude, SBP amplitude, BIS amplitude, PDRA, and remifentanil Ce to

discriminate movers from non-movers upon surgical stimulation was assessed with the area under the receiver operating characteristics curve (AUC). Comparison of the AUCs used the DeLong method.[20] The difference between two AUCs and its 95% CI was estimated by bootstrap resampling (B = 2000) and the percentiles method.

The probability of movement (P) upon surgical stimulation as a function of PDRA evoked by SNT was estimated with a logistic regression model. The binary dependent variable was the occurrence of movement, and the independent variable was the logarithm of PDRA. Calibration of the model used a calibration plot with PDRA divided in four groups based on quartiles (first quartile: PDRA ≤0.18 mm; second quartile: 0.18 mm < PDRA ≤ 0.53 mm; third quartile: 0.53 mm < PDRA ≤ 1.42 mm; fourth quartile: PDRA >1.42 mm). PDRA associated with a 50% probability of nonmovement (PDRA50 corresponding to P = 0.5) upon surgical stimulation was calculated as follows[21]:

$$\log \mathrm{PDRA50} = \frac{\log\left(\frac{p}{1-p}\right) - a}{b}$$

where P is 0.5, a the estimated intercept of the logistic model, and b the estimated slope of the logistic model. PDRA associated with a 95% probability of nonmovement was calculated similarly with P = 0.05. The 95% CI of PDRA50 and PDRA95 were estimated by bootstrap (B = 2000) and the percentiles method. A similar analysis was made for remifentanil Ce to estimate IC50 and IC95.

Results

Between February 7, 2013, and October 22, 2013, 80 patients were included. One patient in each group of remifentanil Ce was excluded: one for laryngospasm before SNT (group 0 ng/ml), one for occlusion of remifentanil infusion line (group 1 ng/ml), one for faulty skin contact with stimulation electrodes (group 3 ng/ml), and one for thoracic rigidity requiring a decrease in remifentanil Ce (group 5 ng/ml). Characteristics of the 76 analyzed patients are presented in table 1.

The mean time elapsed between start of propofol and remifentanil infusions and SNT was 11 ± 8 minutes. Statistically significant changes of HR, SBP, BIS, and PD (tables 2 and 3) were observed upon SNT. For the four groups of remifentanil Ce combined, the relative variation was 33 ± 37% for PD, 2 ± 6% for SBP, 4 ± 9% for HR, and −4 ± 15% for BIS. Even with a remifentanil Ce of 3 and 5 ng/ml, a statistically significant increase in PD was observed upon SNT.

The mean time elapsed between SNT and surgical stimulation was 11 ± 5 min. Twenty-one patients had movements upon surgical stimulation (27.6%): 16 in the 0 ng/ml group, five in the 1 ng/ml group, and zero in the 3 and 5 ng/ml groups. Comparisons of HR amplitude, SBP

Table 1. Characteristics of the 76 Patients and of the Four Groups of Remifentanil Effect-site Concentration

	All Patients (n = 76)	Group 0 ng/ml (n = 19)	Group 1 ng/ml (n = 19)	Group 3 ng/ml (n = 19)	Group 5 ng/ml (n = 19)	*P* Value*
Age (yr)	28 ± 6	29 ± 6	27 ± 6	27 ± 7	29 ± 7	0.49
Height (cm)	166 ± 7	167 ± 6	164 ± 7	167 ± 7	166 ± 6	0.36
Weight (kg)	63 ± 11	65 ± 11	63 ± 12	62 ± 9	62 ± 12	0.81
BMI (kg/m^2)	22.9 ± 3.8	23.5 ± 4.2	23.4 ± 4.0	22.3 ± 3.1	22.6 ± 4.0	0.67
Surgical procedure						0.22
Abortion	67 (88%)	16 (84%)	17 (89%)	19 (100%)	15 (79%)	
Miscarriage	9 (12%)	3 (16%)	2 (11%)	0 (0%)	4 (21%)	
On arrival in the operating room						
Systolic blood pressure (mmHg)	110 ± 12	108 ± 13	107 ± 15	111 ± 8	115 ± 12	0.23
Heart rate (/min)	78 ± 13	77 ± 13	75 ± 16	78 ± 11	83 ± 13	0.34
Bispectral index	96 ± 3	96 ± 3	95 ± 4	96 ± 3	95 ± 2	0.44
Time elapsed between start of propofol and remifentanil infusions and SNT (min)	11 ± 8	12 ± 4	14 ± 15	8 ± 3	10 ± 3	0.16
Time elapsed between SNT and surgical stimulation (min)	11 ± 5	12 ± 6	11 ± 3	11 ± 4	12 ± 6	0.93
Estimated propofol concentration (μg/ml) at loss of consciousness	4.2 ± 0.5	4.4 ± 0.8	4.3 ± 0.5	4.1 ± 0.2	4.1 ± 0.3	0.17
Estimated propofol concentration at loss of consciousness (μg/ml)						0.11
4.0	64 (84%)	15 (79%)	14 (74%)	18 (98%)	17 (89%)	
5.0	8 (11%)	1 (5%)	4 (21%)	1 (5%)	2 (11%)	
5.5	1 (1%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	
6.0	3 (4%)	3 (16%)	0 (0%)	0 (0%)	0 (0%)	

Results are presented as mean (± 1 SD) or number of patients (%).

* *P* value for comparison across the four groups of remifentanil concentration.

BMI = body mass index; SNT = standardized noxious test.

Table 2. Heart Rate, Systolic Blood Pressure, and Bispectral Index Values before and after the Standardized Noxious Test in the 76 Patients and in the Four Groups of Remifentanil Effect-site Concentration

	All Patients (n = 76)	Group 0 ng/ml (n = 19)	Group 1 ng/ml (n = 19)	Group 3 ng/ml (n = 19)	Group 5 ng/ml (n = 19)
SBP (mmHg)					
Before SNT	87 ± 9	90 ± 9	91 ± 9	83 ± 8	83 ± 5
After SNT	88 ± 9	93 ± 10	94 ± 9	82 ± 6	85 ± 5
Amplitude	1 ± 6	2 ± 5	3 ± 8	−1 ± 5	2 ± 5
P value*	0.018	0.03	0.09	0.23	0.055
HR (/min)					
Before SNT	69 ± 12	75 ± 10	69 ± 15	63 ± 8	68 ± 10
After SNT	72 ± 13	82 ± 11	72 ± 17	64 ± 6	69 ± 11
Amplitude	3 ± 6	7 ± 9	2 ± 6	1 ± 3	1 ± 3
P value*	0.0001	0.0023	0.063	0.60	0.10
BIS					
Before SNT	47 ± 12	45 ± 11	49 ± 11	50 ± 11	44 ± 14
After SNT	45 ± 12	47 ± 13	47 ± 12	46 ± 11	40 ± 12
Amplitude	−2 ± 7	2 ± 9	−2 ± 6	−4 ± 5	−5 ± 7
P value*	0.002	0.64	0.15	0.01	0.007

The amplitude is the difference between the value after the standardized noxious test and the value before the standardized noxious test. Results are expressed as mean (±1 SD).

* *P* value for comparisons between after and before SNT within each group of remifentanil concentration.

BIS = bispectral index; HR = heart rate; SBP = systolic blood pressure; SNT = standardized nociceptive test.

Table 3. Pupillary Diameter before and after the Standardized Noxious Test in the 76 Patients and in the Four Groups of Remifentanil Effect-site Concentration

	All Patients (n = 76)	Group 0 ng/ml (n = 19)	Group 1 ng/ml (n = 19)	Group 3 ng/ml (n = 19)	Group 5 ng/ml (n = 19)	*P* Value*	0 *vs.* 1	0 *vs.* 3	0 *vs.* 5	1 *vs.* 3	1 *vs.* 5	3 *vs.* 5
PD before SNT (mm)	2.8 ± 0.9	4.0 ± 1.0	2.6 ± 0.5	2.3 ± 0.2	2.2 ± 0.3	<0.0001	<0.0001	<0.0001	<0.0001	0.29	0.14	0.57
PD after SNT (mm)	3.7 ± 1.7	5.7 ± 1.2	4.1 ± 1.5	2.7 ± 0.6	2.4 ± 0.5	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	0.39
PDRA (mm)	1.0 ± 1.1	1.8 ± 0.9	1.6 ± 1.3	0.4 ± 0.6	0.2 ± 0.4	<0.0001	0.92	<0.0001	<0.0001	0.0002	<0.0001	0.91
P value†	<0.0001	<0.0001	<0.0001	0.0001	0.0001	—	—	—	—	—	—	—

The amplitude or PDRA is the difference between the PD after the SNT and the PD before the SNT. Results are expressed as mean (±1 SD).

* *P* value for comparisons across the four groups of remifentanil effect-site concentration. † *P* value for comparison between after and before SNT within each group of remifentanil effect-site concentration.

PD = pupillary diameter; PDRA = pupillary dilatation reflex amplitude; SNT = standardized noxious test.

amplitude, BIS amplitude, and PDRA evoked by SNT and remifentanil Ce between movers and non-movers upon surgical stimulation are presented in table 4. For the four groups of remifentanil Ce combined, a significant difference was observed between movers and non-movers for SBP amplitude, BIS amplitude, PDRA, and remifentanil Ce (table 4). The highest discriminative ability was observed for remifentanil Ce, with an AUC of 0.94 (95% CI, 0.89 to 0.98) and PDRA with an AUC of 0.90 (95% CI, 0.83 to 0.96), indicating an excellent discrimination for both variables (fig. 2). No significant difference was observed between these two AUCs ($P = 0.29$; mean difference = 0.04 [95% CI, −0.03 to 0.12]). Similar results were observed for remifentanil Ce and PDRA for patients with a remifentanil Ce ≤3 ng/ml (groups 0, 1, and 3 ng/ml combined) and for patients with a remifentanil Ce ≤1 ng/ml (groups 0 and 1 ng/ml combined).

The relationships between PDRA and remifentanil Ce and the probability of movement are presented in figure 3. PDRA associated with a 50% probability of nonmovement upon surgical stimulation was 1.39 mm (95% CI, 0.96 to 2.20) and PDRA95 0.29 mm (95% CI, 0.17 to 0.55). For remifentanil Ce, IC50 was 0.62 ng/ml (95% CI, 0.30 to 0.97) and IC95 1.69 ng/ml (95% CI, 1.05 to 2.33).

Discussion

In this study, PDRA evoked by an SNT was as accurate as the estimated remifentanil Ce to predict movement response upon surgical stimulation.

PDRA evoked by an SNT had a higher relative variation (+33%) than HR, blood pressure, and BIS. This higher dynamic range than the traditionally used hemodynamic parameters is in accordance with previous studies.[22,23] Larson *et al.*[23] reported that the relative variation of PDRA evoked

Table 4. Comparisons and Area under the Receiver Operating Characteristics Curve for Heart Rate Amplitude, Systolic Blood Pressure Amplitude, Bispectral Index Amplitude, and Pupillary Dilatation Reflex Amplitude Evoked by the Standardized Noxious Test or Remifentanil Effect-site Concentration (Ce) between Movers and Non-movers upon Surgical Stimulation at Various Remifentanil Effect-site Concentration

	Groups 0 and 1 ng/ml (n = 38)				Groups 0, 1, and 3 ng/ml (n = 57)				Groups 0, 1, 3, and 5 ng/ml (n = 76)			
	Non-movers (n = 17)	Movers (n = 21)	*P* Value*	AUC (95% CI)	Non-movers (n = 36)	Movers (n = 21)	*P* Value*	AUC (95% CI)	Non-movers (n = 55)	Movers (n = 21)	*P* Value*	AUC (95% CI)
HR amplitude (/min)	3 ± 4	6 ± 10	0.45	0.57 (0.38–0.76)	2 ± 4	6 ± 10	0.088	0.64 (0.47–0.80)	2 ± 4	6 ± 10	0.06	0.64 (0.48–0.80)
SBP amplitude (mmHg)	2 ± 7	4 ± 6	0.40	0.58 (0.39–0.77)	0 ± 6	4 ± 6	0.037	0.67 (0.52–0.82)	1 ± 6	4 ± 6	0.047	0.65 (0.50–0.79)
BIS amplitude	−2 ± 6	2 ± 8	0.13	0.65 (0.46–0.83)	−3 ± 6	2 ± 8	0.015	0.69 (0.55–0.84)	−4 ± 6	2 ± 8	0.008	0.69 (0.56–0.83)
PDRA (mm)	1.2 ± 0.8	2.0 ± 1.2	0.014	0.73 (0.57–0.90)	0.8 ± 0.8	2.0 ± 1.2	<0.0001	0.85 (0.76–0.95)	0.6 ± 0.7	2.0 ± 1.2	<0.0001	0.90 (0.83–0.96)
Remifentanil Ce (ng/ml)	0.8 ± 0.4	0.2 ± 0.4	0.0004	0.79 (0.66–0.92)	2.0 ± 1.1	0.2 ± 0.4	<0.0001	0.90 (0.83–0.97)	3.0 ± 1.7	0.2 ± 0.4	<0.0001	0.94 (0.89–0.98)
P value†	—	—	—	0.58	—	—	—	0.38	—	—	—	0.29

The amplitude is the difference between the value after the standardized noxious test and the value before the standardized noxious test. Results are expressed as mean ± 1SD.

* *P* value for comparison between non-movers and movers. † *P* value for comparison of AUCs for PDRA and remifentanil Ce.

AUC = area under the receiver operating characteristics curve; BIS = bispectral index; Ce = effect-site concentration; HR = heart rate; PDRA = pupillary dilatation reflex amplitude; SBP = systolic blood pressure.

by an electrical SNT on the abdominal skin in anesthetized adults is larger than the changes in HR or blood pressure. Similar results were reported by Constant *et al.*[22] in children. The observed increase in PD evoked by the SNT in the 3 and 5 ng/ml remifentanil groups also suggests that high remifentanil concentrations may not preclude the use of PDRA to assess the nociception/antinociception balance.[10]

The ability of HR, SBP, or BIS amplitudes to discriminate movers from non-movers upon surgical stimulation was low as indicated by an AUC less than 0.7. These values are in the range of the previously reported ones.[17,19,24,25] On the contrary, the AUC for PDRA was 0.9, indicating an excellent discriminative ability for a test.[25] It was not different from the AUC of remifentanil Ce. Because PDRA was not superior to remifentanil Ce in predicting movement upon surgical stimulation, the potential added value of measuring the nociception/antinociception balance with PDRA in clinical practice when the estimated Ce of remifentanil is available may be questioned. However, PDRA may be particularly useful in two situations. The first situation is when estimation of opioid Ce is not available. For instance, whereas many target-controlled infusion for intravenous anesthetics have been approved in Europe, they have not yet been approved by the Food and Drugs Administration in the United States.[3] In this setting, we suggest that the opioid infusion rate could be targeted to keep PDRA below the PDRA95 (0.29 mm) that is greater than 95% of the clinical effect.[26] However, the benefit of targeting an opioid infusion rate within a specified range of PDRA should be evaluated in a validation study. The second situation is in patients where large variability in pharmacokinetics is expected, such as extreme age, extreme weights, or shocked patients.[27–29] In these situations, models may result in overdosage with the risk of hypotension or underdosage with the risks of movement or hemodynamic reaction. In the current study, only healthy young patients were included, and the generalizability to these specific situations requires further investigations.

Some limitations can be addressed to this study. First, some drugs used during anesthesia such as dopaminergic receptor antagonists (droperidol) or anticholinergic drugs (atropine) are known to alter pupil size and block the pupillary dilatation brought about by noxious stimuli. The use of these drugs should be avoided or delayed until the end of anesthesia.[29] Second, the PDRA95 used movement upon surgical stimulation as an endpoint. Because the blockade of the hemodynamic response to a noxious stimulus requires higher opioids concentration than the blockade of movement, titrating opioid concentration on the PDRA95 presented may not ensure the lack of hemodynamic response.[30] Third, surgical stimulation was defined by cervical dilatation and not by skin incision, owing to the characteristics of the surgical procedure. Generalizability of the results requires further validation in other types of surgical procedures. Fourth, the design of this proof of concept study precludes the analysis of the interactions between propofol

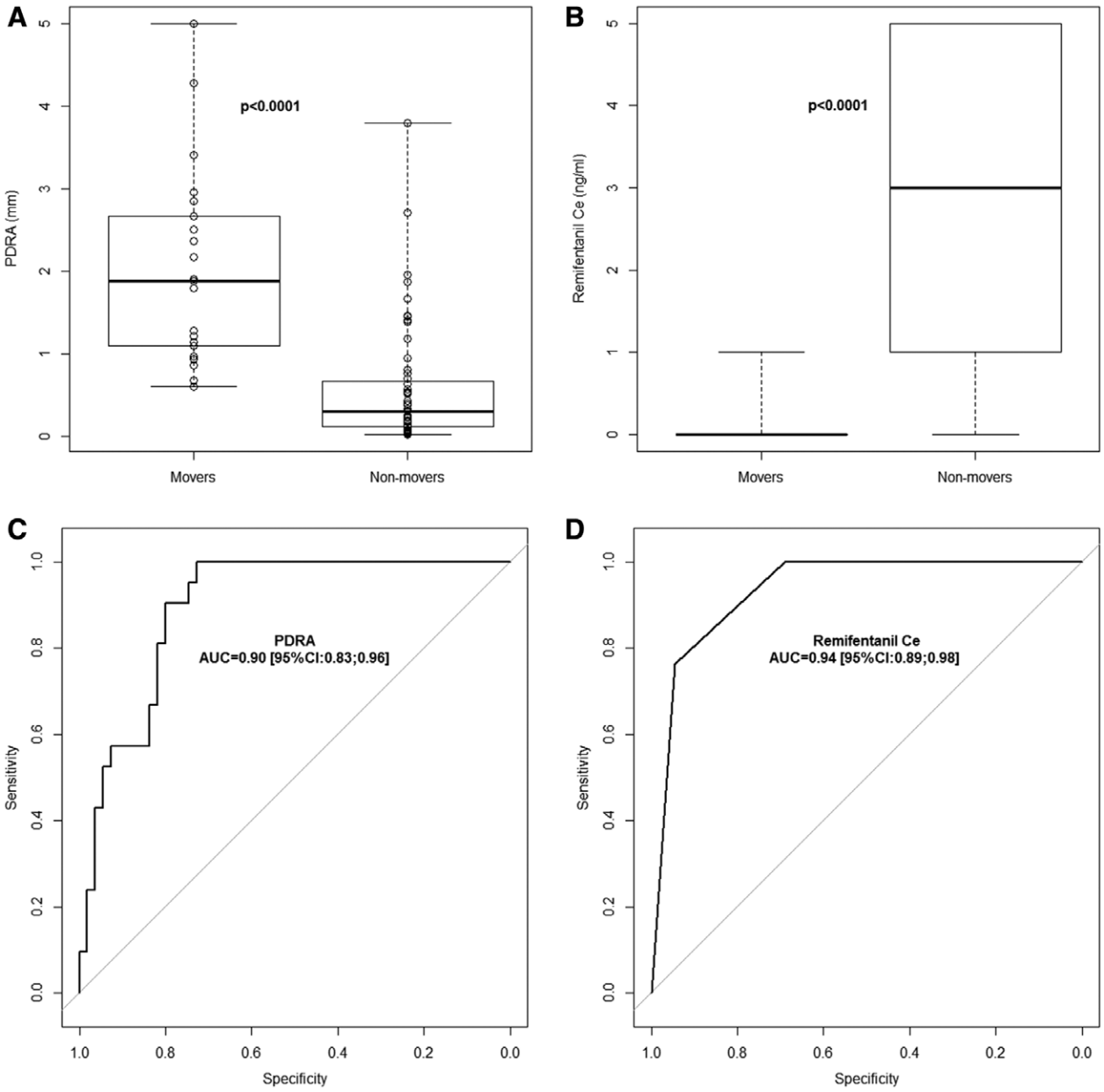

Fig. 2. (*A*) Boxplots of pupillary dilatation reflex amplitude (PDRA) evoked by the standardized noxious test (SNT) and movement upon surgical stimulation. The *thick horizontal line* indicates the median, the *limits of the box* the 25th and 75th percentiles, and the *whiskers* the extreme values. The *unfilled dots* represent the individual values. (*B*) Boxplots of remifentanil effect-site concentration (Ce) and movement upon surgical stimulation. (*C*) Receiver operating characteristic curve for PDRA evoked by the SNT and movement upon surgical stimulation. (*D*) Receiver operating characteristic curve for remifentanil Ce and movement upon surgical stimulation. AUC = area under the receiver operating characteristic curve.

and remifentanil in producing immobility by using a fixed propofol Ce. Although an increase in propofol Ce was permitted if LOC was not obtained at 4 μg/ml, only 12 patients (16%) required such an increase. In addition, the mean propofol Ce was not statistically different across the four groups of remifentanil Ce. To assess the possible hypnotic–opioid interactions in the current study, we calculated the Noxious Stimulation Reactivity Index described by Luginbühl *et al.*[31] The index was significantly higher in movers upon surgical stimulation compared with non-movers (79.6 ± 6.5 *vs.* 61.0 ± 11.4, $P < 0.0001$). The AUC for the index was 0.93 (0.87;0.98) and not statistically different from the AUC for remifentanil Ce (0.94 [0.89;0.98]). These results suggest that taking into consideration hypnotic–opioid interactions in this study would not have improved the prediction. Fifth, we did not use electronic acquisition of hemodynamic and electroencephalographic data in the current study. The 30-s interval between recordings after the SNT was based on the minimal interval between two noninvasive blood pressure measurements. We may have therefore missed the maximum

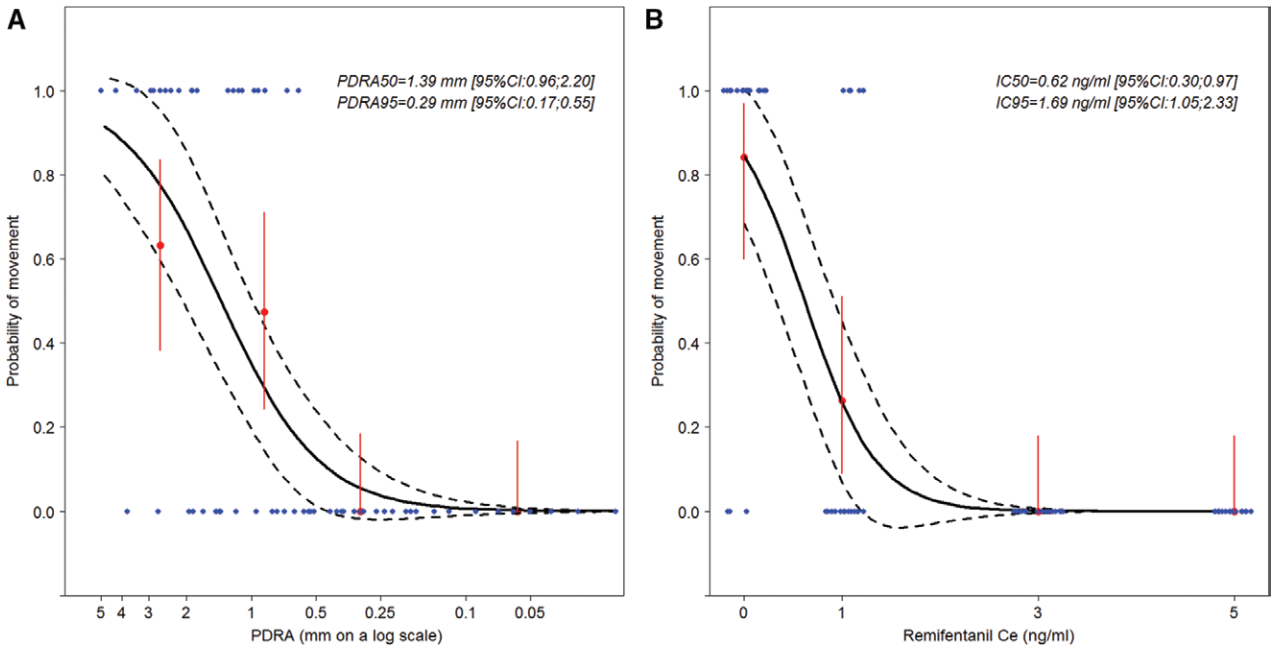

Fig. 3. (*A*) Relationships between pupillary dilatation reflex amplitude (PDRA) evoked by the standardized noxious test and the probability of movement upon surgical stimulation. The *thick black line* indicates the probability of movement upon surgical stimulation and the two *dashed lines* its 95% confidence interval. The *red points* indicate the observed frequencies of movement for each quartile of PDRA with its 95% confidence interval. The individual observations are represented by *blue points* with 1 for movers and 0 for non-movers. (*B*) Relationships between remifentanil effect-site concentration (Ce) and the probability of movement upon surgical stimulation. IC = inhibitory concentration.

change in the surrogate markers that may have underestimated their real performance.

In conclusion, PDRA evoked by SNT is as accurate as remifentanil Ce to predict movement response upon surgical stimulation. Monitoring PDRA during anesthesia could help the anesthesiologist in the decision-making regarding the adaptation of opioids effect-site concentration.

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Competing Interests

The authors declare no competing interests.

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