Patterns of Hysteresis Between Induction and Emergence of Neuroanesthesia are Present in Spinal and Intracranial Surgeries

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Background: Recovery of consciousness is usually seen as a passive process, with emergence from anesthesia depicted as the inverse process of induction resulting from the elimination of anesthetic drugs from their central nervous system sites of action. However, that need not be the case. Recently it has been argued that we might encounter hysteresis to changes in the state of consciousness, known as neural inertia. This phenomenon has been debated in neuroanesthesia, as manipulation of the brain might further influence recovery of consciousness. The present study is aimed at assessing hysteresis between induction and emergence under propofol-opioid neuroanesthesia in humans using estimated propofol concentrations in both spinal and intracranial surgeries.

Methods: We identified the moments of loss (LOR) and recovery of responsiveness (ROR) in 21 craniotomies and 25 spinal surgeries. Propofol was given slowly until loss of responsiveness and stopped at the end of surgery. An opioid was present at induction and recovery. Propofol infused was recorded and plasma and effect-site concentrations were estimated using 2 pharmacokinetic models. Dose-response curves were generated. Estimated propofol plasma and effect-site concentrations were compared to assess hysteresis.

Results: Estimated propofol concentrations at LOR and ROR showed hysteresis. Whether for spinal or intracranial surgeries, the EC_{50} of propofol at which half of the patients entered and exited the state of responsiveness was significantly different.

Conclusions: Hysteresis was observed between propofol concentrations at LOR and ROR, in both patients presenting for spinal and intracranial surgeries. Manipulation of the brain does not appear to change patterns of hysteresis, suggesting that neural inertia may occur in humans, in a way similar to that found in animal species. These findings justify performing a clinical study in patients using measured propofol concentrations to assess neural inertia.

Key Words: general anesthesia, propofol, opioid, hysteresis, intracranial surgeries, spinal surgeries, Marsh, Schnider, estimations

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Recovery of consciousness and responsiveness (ROR) has been viewed for many years as the inverse process of anesthetic induced loss of responsiveness (LOR).[1] However, accumulating evidence suggests that this might not be the case. Consequently, debate whether the asymmetry between the anesthetic concentrations required for induction and emergence (anesthetic hysteresis) is because of pharmacokinetic characteristics or intrinsic neural mechanisms persists.[2] Increased understanding of the mechanisms enabling anesthetic emergence, could eventually convert today's passive clinical approach into a pharmacological intervention to actively modulate arousal.[1,3]

The hysteretic dissociation of anesthetic induction from emergence was first described in mice and fruit flies,[2,4] with lower concentrations of anesthetics required for emergence. This hysteresis could not be explained solely by pharmacokinetics and the existence of a barrier termed "neural inertia" was proposed. The neural inertial barrier promotes maintenance of wakefulness or anesthesia and presumably exists to oppose rapid and potentially catastrophic transitions between these states.

Evidence supporting or refuting hysteresis with general anesthesia in humans has since been investigated.

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Three recent studies[5–7] have sought to clarify this by measuring dose-response curves for emergence and induction of general anesthesia. However, evidence remains to be conclusive, with neural inertia being observed in humans only under some circumstances. Kuizenga et al[5] found evidence supporting neural inertia with some sevoflurane-based regimens but intriguingly, not with propofol. In the Warnaby study with volunteers who received only propofol, showing evidence supporting neural inertia using predicted propofol concentrations at loss and return of conscious also failed. Nevertheless, Warnaby and colleagues demonstrate that EEG slow wave activity saturation was asymmetric during induction and emergence. They suggest that slow wave activity saturation might be a signature of neural inertia in humans. In the study by Sepúlveda et al,[7] hysteresis between loss and recovery of responsiveness in volunteers with propofol was observed, although they stated their results cannot definitively confirm the presence of neural inertia. Some of these studies suggest that hysteresis is not likely because of pharmacokinetic mechanisms alone but might be explained by different pathways and neural circuits that drive the hypnotic effects of each drug. However, study designs could influence the detection of neural inertia and lead to false positive results.[8]

The asymmetry between LOR and ROR has also been discussed in neuroanesthesia but regarding the influence of surgical manipulation of the brain during intracranial procedures and if changes in intracranial pressure might influence hysteresis. To clarify this, we conducted a clinical study in patients presenting for intracranial and spinal surgeries under propofol and opioid anesthesia. Under a well-defined clinical protocol, estimated propofol plasma (Cp) and effect-site (Ce) concentrations were determined to assess hysteresis at the moment of LOR and ROR by applying both the Schnider's and the Marsh's pharmacokinetic (PK) models. Neurosurgical patients requiring both craniotomies for excision of brain tumors and spinal surgeries were specifically included to evaluate if the estimated concentrations at LOR and ROR would differ between intracranial and spinal procedures.

METHODS

Anesthetic Protocol

Under institutional review board approval and written informed consent, consecutive adult patients undergoing routine neurosurgical procedures, expected to last for >90 minutes, were anesthetized as described below. Craniotomies were performed both for supra and infratentorial tumors. Spinal surgeries included laminectomies, decompressions, and fusions. Dates of enrollment were from March 2016 to July 2016.

Exclusion criteria were: any alterations in mental status or BIS < 90 before induction, significant cardiovascular, renal, hepatic, or respiratory pathology, and obesity (BMI > 35 kg/m^2). Procedures done by the same anesthesiologist over a 5-month period were included.

None of the patients was premedicated. In the operating room, after placement of standard monitors and placement of an intravenous line in the dorsum of the hand, an infusion of an equilibrated electrolytic solution was started at 6 mL/kg/h. Our clinical practice for neurosurgical procedures consists of opioid-propofol anesthesia using a Target Controlled Infusion (TCI) system. Anesthesia began with a fentanyl bolus of 3 μg per kg of ideal body weight (IBW). Four minutes later, a tourniquet was applied to the arm 20 cm above the venous catheter and a bolus of 20 mg of lidocaine was administered to reduce the pain associated with propofol and the limb withdrawal responses associated with rocuronium.[9,10] Propofol was administered using a Fresenius Base Primea docking station (Fresenius-Kabi, Bad Homburg, Germany) with 2 Fresenius Module DPS pumps. Intravenous infusion of 1% propofol started at 3.3 mL/kg/h. This slow velocity of infusion during induction enables a careful titration of the minimum amount of propofol required for LOR and allows for precise documentation of the moment of loss of consciousness. By using a TCI enabled device, estimated drug concentrations are constantly processed and displayed with 1-second iterations. Once propofol reached the venous catheter, the tourniquet was released. The level of consciousness was assessed every 10 seconds using the Modified Observer's Assessment of Anesthesia and Sedation (OAA/S) scale.[11] At this point, no additional analgesic/opioid medication was given during induction. At LOR, defined as an OAA/S score of zero (lack of response to name calling and compression of the trapezius on the shoulder) the propofol infusion was stopped. The amount of propofol given (in mg) and the Ce and Cp were noted and the Fresenius Base Primea system was switched to effect-site TCI mode, with a target Ce lower than the Ce at LOR through the application of a previously presented formula, developed by our group. Manual ventilation was started, a neuromuscular block monitor (Train-of-Four—TOF) was calibrated and rocuronium was then administered at 0.6 mg/kg. When no responses from TOF were present (TOF equal to 0), laryngoscopy and intubation were performed. After intubation, propofol was titrated to maintain Bispectral Index (BIS) between 40 and 60. Remifentanil by TCI was started 30 minutes after LOR and titrated during surgery. Propofol, fentanyl and remifentanil Ce were calculated using Schnider's,[12] Shafer's[13] and Minto's[14] pharmacokinetic (PK) models, respectively. At the end of surgery, remifentanil Ce was fixed at 2.0 ng/mL and propofol infusion was stopped. The patient was called in a loud voice every 10 seconds and told to open his/her eyes. The moment of eye-opening was considered the moment of ROR. At that exact moment, the propofol Ce and Cp and the total amount of propofol given were recorded. The infused volumes data was used to estimate Ce and Cp with Marsh's PK model. Data recording was performed using Rugloop software (Demed, Genk, Belgium), installed on a dedicated computer. This software communicates with Datex/GE monitor, BIS monitor, and Fresenius Base Primea system. Rugloop software collects data every 5 seconds. Data collection ended 10 minutes following extubation.

Statistical Methods

To determine the primary endpoint and evaluate for potential hysteresis between induction and emergence in

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patients presenting for neuroanesthesia, we relied on the study of Nunes et al[15] that showed an average paired difference between the estimated Ce concentrations of propofol at LOR and ROR of 3.73 ± 0.92 μg/mL. Importantly, however, opioids were not present at LOR in the Nunes study.[15] In the present study, since an opioid was present at induction, it was expected that the propofol concentration required for LOR would be smaller and, therefore the expected difference between concentrations of propofol at LOR and ROR would also be smaller. Sample size calculation was performed to detect a difference of 1 μg/mL, with 95% power, $\alpha = 1\%$ and the same 0.92 SD of the paired response difference[15] (Sample size paired *t* test, StatsDirect V3). A minimum sample size of 19 pairs/patients was obtained. Considering the 2 types of procedures performed in neurosurgery (craniotomies and spinal surgeries) and considering a 20% exclusion rate, a final samples size of 46 patients was established.

Propofol estimated concentrations at LOR and at ROR were analyzed and compared in all the patients, and in each of the 2 subgroups of surgical procedures: craniotomies and spinal surgeries. Following the assessment of the primary hypothesis, the second step was to determine the dose-response curves.

To generate the dose-response curves for LOR and ROR, propofol Ce data at LOR were sorted from the lowest to the highest value in order to obtain the percentage of awake patients for each specific concentration. Constraints were used when determining all dose-response curves such that at the highest propofol Ce all patients were assumed unconscious and in the absence of propofol, all patients were assumed to be conscious. Both of these assumptions prove experimentally valid. Dose-responses curves for LOR and ROR were then generated for the entire group of patients and for the 2 subgroups. To adjust the response curves to our data, sigmoidal dose-response and variable slope function as described elsewhere[2,16] were used. This nonlinear regression model parameters were: the bottom and top plateaus of the curve, representing the minimum and maximum values of the percentage of awake patients; the EC_{50}, representing the concentration of that drug at which 50% of the effect was observed; and the Hill's slope representing the steepness of the curve. This curve was symmetrical around its inflection point, which was defined as the point on the curve where the curvature changes direction. The bottom was set to 0 and top to 100. No constraints were placed on the Hill's slope or EC_{50} fit parameters.

The third step was to calculate the area between the LOR and ROR sigmoidal dose-response curves. For that, both LOR and ROR sigmoidal dose-response curves were mathematically integrated over the range of the LOR curve EC_1 (the concentration at which 1% of the patients had not yet entered into anesthetic state) to the ROR curve EC_{99} (the concentration at which 99% of the patients had exited the anesthetic state), as detailed elsewhere.[2] This integration yielded an area (difference between the integrated LOR sigmoidal dose-response curve and the integrated ROR curve) that is a unit-less quantitative measure of the resistance to transitions between arousal states, which is, by definition, neural inertia.

All previous steps were repeated using propofol concentrations as estimated by the Marsh's PK model.

Propofol Cp and Ce values for the Marsh's PK model were estimated using the infused propofol volumes recorded at 5 seconds intervals during each case.

Paired variables were compared with the Student *t* test or the Wilcoxon matched pairs test as appropriate for the data distribution. Correlation analyses were performed using the Spearman's or the Pearson's method as appropriate for the data distribution. Comparisons between data from patients presenting for intracranial and spinal surgeries were performed with the Student *t* test for independent samples or Mann-Whitney, depending on the data distribution. Comparison of neural inertia obtained between models was performed with one-way ANOVA.

A *P*-value <0.01 was considered statistically significant.

Results are presented as mean ± SD or mean [95% CI: lower limit, upper limit] for the normally distributed variables and as median (P25-P75) for the non-normally distributed variables (explicitly mentioned).

Statistical analysis was performed using MATLAB® 2014a (Mathworks Inc., Natick, MA) and IBM SPSS Statistics (IBM Corporation, NY).

RESULTS

A total of 46 neurosurgical patients were included in this study, 25 presenting for spinal surgery and 21 presenting for intracranial surgery. One patient presenting for intracranial surgery was excluded from the analysis due to an error in data recording, therefore, data from 45 patients are presented. Demographics for all 45 patients were: 58 ± 13 years of age, 68 ± 12 kg, 164 ± 8 cm, 25 ± 4 BMI, 20 males and 25 females, 4 ASAI, 31 ASAII, and 10 ASAIII. Demographics for the 20 patients presenting for craniotomies were: 55 ± 16 years of age, 67 ± 11 kg, 166 ± 8 cm, 24 ± 4 BMI, 9 males and 11 females, 1 ASAI, 13 ASAII, and 6 ASAIII. Demographics for the 25 patients presenting for spinal surgeries were: 60 ± 10 years of age, 69 ± 13 kg, 163 ± 7 cm, 26 ± 4 BMI, 12 males and 13 females, 3 ASAI, 18 ASAII, and 4 ASAIII. There were no statistically significant differences in demographic data between patients presenting for craniotomies and spinal surgeries (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/JNA/A81).

Estimated propofol, fentanyl and remifentanil plasma and effect-site concentrations at LOR and ROR for all surgeries and for the subgroups of craniotomies and spinal surgeries are presented in Table 1, results expressed with regard to the 95% Confidence Intervals (CI) for the sample mean. For the moment of LOR and considering all surgeries, estimated effect-site drug concentrations were: fentanyl 3.48 [3.38; 3.58] ng/mL, propofol 4.04 [3.58; 4.50] μg/mL using the Schnider's PK model and 2.92 [2.58; 3.25] μg/mL using the Marsh's PK model. For the moment of ROR, estimated effect-site concentrations were: for

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TABLE 1. Propofol, Fentanyl, and Remifentanil Estimated Concentrations at LOR and ROR in All 45 Patients, in the Patients Subjected to Craniotomies Only and in Patients Submitted to Spinal Surgeries

	All Surgeries		Intracranial Surgeries		Spinal Surgeries	
	LOR (n = 45)	ROR (n = 45)	LOR (n = 20)	ROR (n = 20)	LOR (n = 25)	ROR (n = 25)
Ce propofol (Schnider) (μg/mL)	4.04 [3.58; 4.50]	1.09 [0.98; 1.20]	3.93 [3.25; 4.62]	1.11 [0.93; 1.28]	4.12 [3.46; 4.79]	1.08 [0.93; 1.23]
	2.94 [2.52; 3.36]		2.82 [2.18; 3.47]		3.04 [2.45; 3.64]	
	$P < 0.001$		$P < 0.001$		$P < 0.001$	
Cp propofol (Schnider) (μg/mL)	8.40 [7.94; 8.86]	0.88 [0.79; 0.97]	8.09 [7.32; 8.86]	0.96 [0.80; 1.11]	8.65 [8.07; 9.22]	0.82 [0.70; 0.93]
	7.52 [7.08; 7.97]		7.14 [6.38; 7.90]		7.83 [7.29; 8.37]	
	$P < 0.001$		$P < 0.001$		$P < 0.001$	
Ce propofol (Marsh) (μg/mL)	2.92 [2.58; 3.25]	1.34 [1.21; 1.48]	2.92 [2.40; 3.44]	1.39 [1.15; 1.64]	2.91 [2.44; 3.38]	1.30 [1.14; 1.46]
	1.57 [1.26; 1.89]		1.52 [1.06; 1.99]		1.61 [1.16; 2.06]	
	$P < 0.001$		$P < 0.001$		$P < 0.001$	
Cp propofol (Marsh) (μg/mL)	4.09 [3.78; 4.39]	1.27 [1.15; 1.39]	4.08 [3.60; 4.56]	1.33 [1.10; 1.56]	4.09 [3.67; 4.51]	1.22 [1.08; 1.36]
	2.81 [2.54; 3.09]		2.75 [2.32; 3.17]		2.87 [2.47; 3.26]	
	$P < 0.001$		$P < 0.001$		$P < 0.001$	
Ce fentanyl (Shafer) (ng/mL)	3.48 [3.38; 3.58]	0.30 [0.29; 0.32]	3.55 [3.38; 3.72]	0.28 [0.25; 0.32]	3.44 [3.31; 3.56]	0.32 [0.30; 0.34]
Cp fentanyl (Shafer) (ng/mL)	2.11 [2.04; 2.18]	0.30 [0.28; 0.32]	2.16 [2.03; 2.29]	0.28 [0.24; 0.31]	2.07 [1.99; 2.15]	0.31 [0.30; 0.33]
Ce remifentanil (Minto) (ng/mL)	—	2.06 [1.99; 2.13]	—	2.01 [2.00; 2.02]	—	2.11 [1.96; 2.14]
Cp remifentanil (Minto) (ng/mL)	—	2.03 [1.98; 2.08]	—	2.01 [2.00; 2.02]	—	2.05 [1.96; 2.14]

Comparisons were made between the concentrations at LOR and ROR, mean difference and 95% confidence intervals are presented (statistically significant differences $P < 0.01$, paired Student t test).

LOR indicates loss of responsiveness; ROR, recovery of responsiveness.

fentanyl 0.30 [0.29; 0.32] ng/mL, for remifentanil 2.06 [1.99; 2.13] ng/mL, and for propofol 1.09 [0.98; 1.20] μg/mL using the Schnider's PK model and 1.34 [1.21; 1.48] μg/mL using the Marsh's PK model. Estimated plasma concentrations for the same drugs, at the same moments and using the same PK models are presented in Table 1. Opioid and propofol estimated concentrations in patients presenting for craniotomies and patients presenting for spinal surgeries are discriminated in Table 1 as well. Estimated propofol concentrations for all patients at LOR were, on average, 2.94 [2.52; 3.36] μg/mL higher than the concentrations at ROR, using the Schnider's PK model. Propofol estimated concentrations at LOR were always significantly higher than estimated concentrations at ROR, both for plasma and effect-site concentrations, using either the Schnider's or the Marsh's PK models and for comparisons within each of the 2 subgroups of patients (Table 1).

The average time from the moment propofol infusion was started until LOR (2.29 ± 0.75 min) versus the estimated propofol Ce at LOR, the estimated propofol Ce concentrations at LOR versus at ROR for each patient and the average time from the moment propofol infusion was stopped until ROR (6.30 ± 3.86 min) versus the estimated propofol Ce at ROR and versus the estimated propofol Ce when propofol infusion was stopped are shown in Supplemental Figure 1 (Supplemental Digital Content 2, http://links.lww.com/JNA/A82).

The average duration of anesthesia, considered as the time elapsed from LOR until stopping the propofol infusion was 3.40 [2.85; 3.94] hours, with anesthesia for craniotomies lasting significantly longer than for spinal procedures ($P < 0.001$) (Table 2). Propofol average estimated effect-site concentration for the maintenance phase of anesthesia was 1.79 [1.48; 2.09] μg/mL, for craniotomies it was 1.93 [1.35; 2.51] μg/mL and for spinal surgeries it was 1.67 [1.33; 2.01] μg/mL, not statistically different ($P = 0.421$, Student t test for independent samples). At the moment propofol infusion was stopped following the end of surgeries, estimated propofol Ce for

TABLE 2. Propofol and Remifentanil Estimated Effect-site Concentrations During Maintenance, Propofol Estimated Effect-site Concentration When Infusion was Stopped Before the End of the Procedure and Duration of the Procedure

	All Surgeries (n = 45)	Intracranial Surgeries (n = 20)	Spinal Surgeries (n = 25)
Ce propofol (Schnider) during maintenance (μg/mL)	1.79 [1.48; 2.09]	1.93 [1.35; 2.51]	1.67 [1.33; 2.01]
		0.26 [−0.36; 0.88]; $P = 0.421$	
Ce propofol (Schnider) when infusion is stopped (μg/mL)	2.06 [1.87; 2.25]	2.06 [1.75; 2.37]	2.06 [1.80; 2.32]
		0.001 [−0.39; 0.39]; $P = 0.994$	
Ce remifentanil (Minto) during maintenance (ng/mL)	1.69 (1.35-2.72)*	2.55 (1.50-3.81)*	1.44 (1.30-1.89)*
		$P = 0.005$	
Duration of the procedure (h)	3.40 [2.85; 3.94]	4.52 [3.49; 5.56]	2.50 [2.30; 2.70]
		2.02 [0.97; 3.07]; $P < 0.001$	

Comparisons between craniotomies and spinal surgeries are presented (Student t test or Mann-Whitney).

$P < 0.01$ represents a statistic significant difference.

*Results are presented as median (P25-P75).

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all patients was 2.06 [1.87; 2.25] μg/mL, for craniotomies it was 2.06 [1.75; 2.37] μg/mL and for spinal surgeries it was 2.06 [1.80; 2.32] μg/mL, not statistically different ($P = 0.994$, Student t test for independent samples). Remifentanil estimated effect-site concentration during anesthesia maintenance for all patients was 1.69 (1.35 to 2.72) ng/mL, with the Ce for craniotomies being significantly higher than those for spinal surgeries ($P = 0.005$, Mann-Whitney test). Mean arterial pressure at ROR was significantly higher than at LOR, but heart rate at LOR and ROR and end-tidal CO_2 at LOR (second breath after tracheal intubation) and ROR were similar (Supplemental Table 2, Supplemental Digital Content 3, http://links.lww.com/JNA/A83). Arterial pressure, heart rate and end-tidal CO_2 at both LOR and ROR did not differ between patients presenting for craniotomies and spinal surgeries. Intraoperative blood loss did not mandate a blood transfusion in any patient.

The goodness-of-fit measures for the LOR and ROR sigmoidal dose-response curves were the adjusted R-squared (coefficient of determination) which ranged from 0.97 to 0.99 and the root mean squared error which ranged from 2.60 to 5.10 with a median value of 3.93. These values showed an overall very good fit to the data. In Table 3 are displayed the EC_{50} and the Hill's slope parameters obtained from the fitting of the nonlinear regression models. All values are reported along with their corresponding 95% CI. Propofol concentrations at which half of the patients entered and exited the state of responsiveness for induction were always statistically significantly greater than those at emergence ($P < 0.001$), that is, LOR (EC_{50}) > ROR (EC_{50}), for all patients, in the patients presenting for craniotomies and in the patients presenting for spinal surgeries (Table 3). These differences in the EC_{50} between LOR and ROR occurred using concentrations estimated using either the Schnider's and the Marsh's PK models (Table 3).

A more comprehensive description of the differences between propofol Ce concentrations (with the Schnider's PK model) at LOR and ROR is shown graphically by the shaded area between the dashed LOR and the solid ROR curves in Figure 1. The dose-response curves presented in Figure 1 considered the best-fit parameters of the nonlinear regression model.

Taking into account that both the Schnider's and the Marsh's PK models achieved sufficient bias and precision in prediction of target concentration,[17–19] we performed an extensive set of bootstrapping simulations using the published median performance errors by Glen and White,[17] so as to establish the error margins for our estimated propofol Cp at LOR and ROR and observe whether hysteresis would still occur. In Figure 2, the propofol dose-response curves are presented considering 1000 simulations of the LOR and ROR concentrations for all patients, for the patients presenting for craniotomies and for the patients presenting for spinal surgeries. As it is observed in the graphs, hysteresis is still present, even when prediction errors of more than 50% are incorporated, which is the case at increasing concentrations for the Marsh's PK model.[17]

DISCUSSION

The present study sought to determine whether a propofol-opioid anesthetic produces detectable neural inertia in a clinical setting and whether neural inertia might be affected by intracranial surgical procedures. We determined that in these neurosurgical patients, presenting for procedures under total intravenous anesthesia, it is possible to observe a pattern of anesthetic hysteresis

TABLE 3. Best-fit Parameters for LOR and ROR Sigmoidal Dose-response Curves Regarding All, Intracranial, and Spinal Surgeries

	All Surgeries		Intracranial Surgeries		Spinal Surgeries	
	LOR (n = 45)	ROR (n = 45)	LOR (n = 20)	ROR (n = 20)	LOR (n = 25)	ROR (n = 25)
Ce Schnider						
Hill's slope	−3.87 [−4.08; −3.67]	−4.68 [−4.98; 4.38]	−4.72 [−5.34; −4.10]	−5.81 [−6.59; −5.02]	−3.61 [−4.02; −3.20]	−4.17 [−4.61; −3.72]
P	< 0.001		0.040		0.078	
EC_{50}	3.92 [3.87; 3.97]	1.08 [1.07; 1.10]	4.09 [3.99; 4.20]	1.13 [1.11; 1.16]	3.92 [3.79; 4.05]	1.06 [1.04; 1.09]
P	< 0.001		< 0.001		< 0.001	
Cp Schnider						
Hill's slope	−10.41 [−11.04; −9.78]	−4.98 [−5.27; −4.68]	−9.19 [−10.6; −7.81]	−5.30 [−6.02; −4.58]	−11.1 [−12.43; −9.77]	−5.60 [−6.16; −5.04]
P	< 0.001		< 0.001		< 0.001	
EC_{50}	8.31 [8.27; 8.35]	0.86 [0.85; 0.87]	8.19 [8.08; 8.30]	0.97 [0.95; 0.99]	8.47 [8.38; 8.55]	0.80 [0.79; 0.82]
P	< 0.001		< 0.001		< 0.001	
Ce Marsh						
Hill's slope	−3.76 [−3.97; −3.55]	−4.85 [−5.10; −4.60]	−4.41 [−5.07; −3.75]	−5.09 [−5.54; −4.63]	−3.64 [−3.97; −3.30]	−4.81 [−5.31; −4.32]
P	< 0.001		0.108		< 0.001	
EC_{50}	2.82 [2.78; 2.86]	1.30 [1.29; 1.31]	3.01 [2.92; 3.10]	1.37 [1.34; 1.39]	2.77 [2.70; 2.84]	1.28 [1.25; 1.31]
P	< 0.001		< 0.001		< 0.001	
Cp Marsh						
Hill's slope	−6.02 [−6.33; −5.71]	−5.07 [−5.35; −4.79]	−7.02 [−7.99; −6.04]	−5.11 [−5.50; −4.71]	−5.81 [−6.32; −5.30]	−5.15 [−5.69; −4.60]
P	< 0.001		0.001		0.088	
EC_{50}	4.07 [4.04; 4.10]	1.24 [1.22; 1.25]	4.22 [4.15; 4.29]	1.31 [1.29; 1.32]	4.03 [3.97; 4.09]	1.21 [1.18; 1.23]
P	< 0.001		< 0.001		< 0.001	

Results are expressed with regard to the 95% confidence intervals for the sample mean (statistically significant differences $P < 0.01$, paired Student t test).
LOR indicates loss of responsiveness; ROR, recovery of responsiveness.

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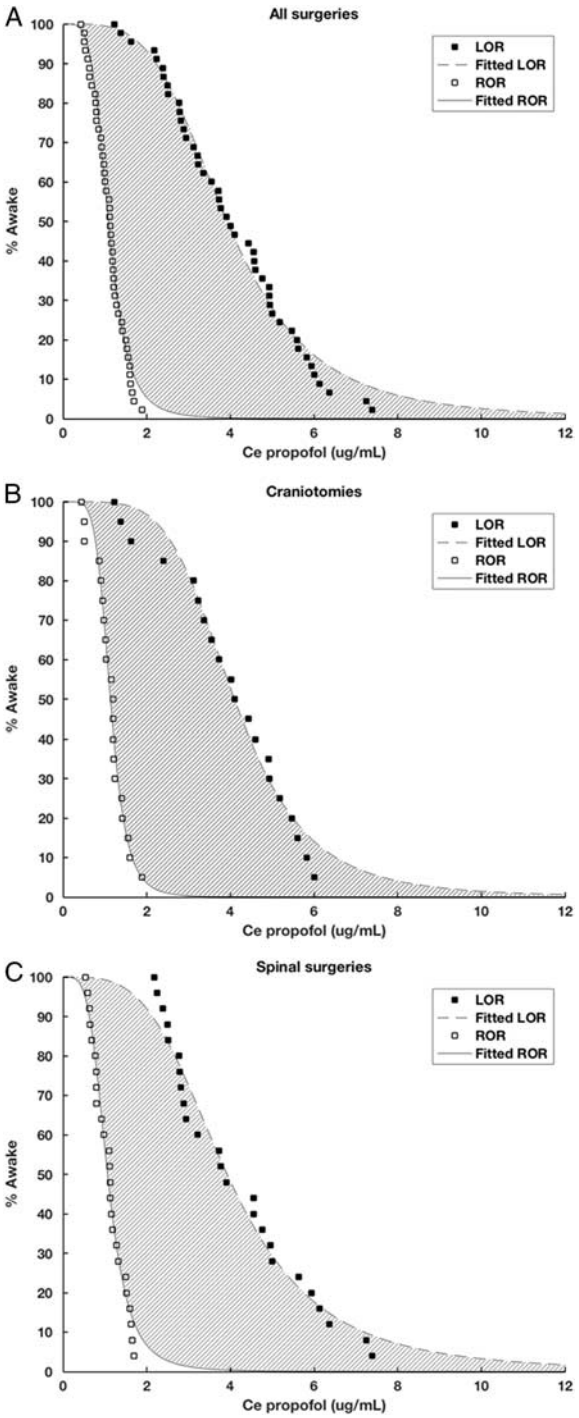

FIGURE 1. Hysteresis. Filled squares and their corresponding best-fit solid curve denote LOR. Open squares and their corresponding best-fit solid curve denote ROR. Within the shaded areas, patients will be awake or anesthetized depending upon their previous state of arousal. These areas represent a resistance to change in the state of consciousness. (A) Propofol dose-response curve in humans for LOR and ROR regarding all surgeries. (B) Propofol dose-response curve in humans for LOR and ROR regarding craniotomies only. (C) Propofol dose-response curve in humans for LOR and ROR regarding spinal surgeries only. LOR indicates moments of loss; ROR, recovery of responsiveness.

consistent with neural inertia. Moreover, manipulation of the human brain in our clinical setting, did not change any of our findings as patients presenting for spinal procedures had indistinguishable anesthetic responses when compared with those needing intracranial resections.

Our data showed that estimated propofol at EC_{50} for induction was greater than at EC_{50} for emergence, suggesting that emergence from anesthesia might not be the opposite mirror process of induction. However, this observation could be due to the use of effect-site target-controlled infusion systems to calculate the infusion regimen and estimating the effect-site concentration instead of measuring them.[8] Nevertheless, the Hill slopes in our studies indicate the same variability between the anesthetic concentrations at induction and emergence in both intracranial and spinal surgeries.

The design of our study was unfortunately suboptimal to address the question of whether the hysteresis is due to pharmacokinetic mechanisms or intrinsic neural mechanisms. First, these results are partially confounded because at induction, our patients received fentanyl before the propofol infusion and then remifentanil for the maintenance phase and until emergence. Despite the fact that, from the point of view of its kinetic-dynamic dissociation, a bolus of fentanyl could not be comparable with TCI remifentanil, from the point of view of its kinetic-dynamic dissociation, theoretically, it would be in Cp equipotent according to the literature reference.[20,21] We modeled the fentanyl concentrations at the moments of LOR and ROR, considering the relationship in potency among opioids, and, opioid concentrations at those moments can be considered clinically equipotent. Also, the measurements we used to calculate hysteresis were based on estimated and not measured propofol concentration. We performed estimations with the Marsh's and the Schnider's PK models and for both plasma and effect-site estimates. Having measured real plasma concentrations at both LOR and ROR would have provided stronger evidence in favor or against hysteresis. However, our analysis of the results applies caution and is performed addressing the limitations of using modeled concentrations. Such limitations may be due to the known errors that have been identified when comparing estimated with real concentrations,[17] with the knowledge that such errors tend to increase during the dynamic phases of anesthesia (induction and recovery) and with the known differences in pharmacokinetic models when estimating propofol concentrations. To check these, we performed an extensive set of simulations considering the prediction errors for our estimated plasma concentrations at LOR and ROR. In our results, patterns of hysteresis are still present even when prediction errors of more than 50% are incorporated. Finally, our results focus on the estimated propofol concentrations at LOR and ROR, but these moments depend not only on the effect of propofol but also on the opioids' effects, given the known synergism between both drugs. Despite this, our study offers the advantage of addressing the real scenario of clinical anesthesia with concomitant surgical intervention. Other factors that could impact on the transitions between responsiveness and unresponsiveness are related to physiological variables that impact on anesthetic delivery to the brain, namely cardiac output, and cerebral blood flow.

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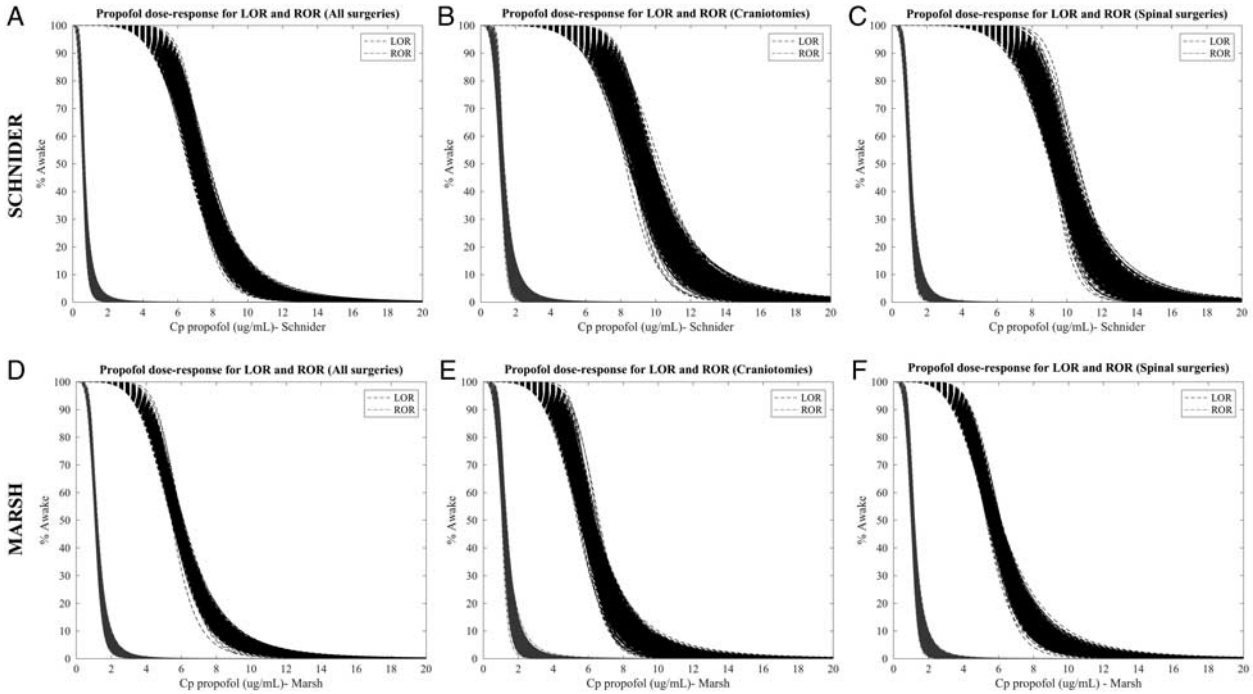

FIGURE 2. Simulation of 1000 propofol dose-response curves for estimated plasma concentrations at LOR and ROR, applying the prediction error margins [Interquartile Range (IQ)] published by Glen and White[17] and considering the difference for increasing and decreasing concentrations (LOR vs. ROR). At the top are presented the propofol dose-response curves for LOR and ROR with plasma concentrations estimated by the Schnider model and at the bottom are presented those by the Marsh model. (A) and (D) All patients; (B) and (E) Patients presenting for intracranial surgeries; (C) and (F) Patients presenting for spinal surgeries. LOR indicates moments of loss; ROR, recovery of responsiveness.

Although none of these variables was measured directly, end-tidal CO_2, which could alter cerebral blood flow, did not differ between LOR and ROR, while heart rate and blood pressure, that can be related to cardiac output, showed heart rate to be the same at LOR and ROR but mean arterial pressure to be significantly lower at ROR, implying that at ROR cardiac output could be lower. Although cardiac output clearly influences the way anesthetics reach the brain, the implication of cardiac output on the brain dynamics of propofol exiting the brain, if indeed that phenomenon happens, remains to be understood.

Despite the concerns previously described and in support of our findings, hysteresis was present in a similar way in both craniotomies and spinal surgeries. Statistically, the only differences between patients having spinal and intracranial surgeries in our results were in anesthesia duration and in the amount of remifentanil required during maintenance. Such differences are not expected to interfere with the main findings.

There were some differences in our study when compared with other studies that assessed neural inertia,[2,5,7] namely at ROR, in which our patients were under significant nociceptive stimulation. At ROR, our patients still had a tracheal tube in place and had just finished a surgical procedure that left them with a surgical wound. This incision was not present at LOR when no nociceptive stimulation was present. These stimuli present at the end of surgery could contribute to some arousal and consequently to higher concentrations of propofol at ROC. Although these studies are aimed to assess the existence of neural inertia in humans, our data pertains to patients undergoing longer anesthetics for surgical procedures. Duration of anesthesia might also have some influence in the presence of hysteresis.

Our results show that independently of neural inertia existing in humans, intracranial procedures do not change hysteresis. Nevertheless, better understanding the switching between consciousness and unconsciousness is of uttermost importance. Acknowledging the existence of a wide inter-patient variability in drug requirements for LOR as well as the existence of hysteresis between drug concentrations at LOR and ROR, could result in an important step towards the implementation of personalized medicine to anesthesiology.

Therefore, we propose a next step should be a study in humans, presenting for surgery under general anesthesia performed with propofol and maintain the same concentration of opioid at LOR and ROR, with plasma propofol and opioid measurements performed at several stages and very precise identification of the moments of LOR and ROR.

REFERENCES

1. Tarnal V, Vlisides PE, Mashour GA. The neurobiology of anesthetic emergence. *J Neurosurg Anesthesiol*. 2015;28:250–255.
2. Friedman EB, Sun Y, Moore JT, et al. A conserved behavioral state barrier impedes transitions between anesthetic-induced unconsciousness and wakefulness: evidence for neural inertia. *PLoS One*. 2010;5:e11903.

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3. Kenny JD, Chemali JJ, Cotten JF, et al. Physostigmine and methylphenidate induce distinct arousal states during isoflurane general anesthesia in rats. *Anesth Analg*. 2016;123:1210–1219.
4. Joiner WJ, Friedman EB, Hung H-T, et al. Genetic and anatomical basis of the barrier separating wakefulness and anesthetic-induced unresponsiveness. *PLoS Genet*. 2013;9:e1003605.
5. Kuizenga MH, Colin PJ, Reyntjens KMEM, et al. Test of neural inertia in humans during general anaesthesia. *Br J Anaesth*. 2018; 120:525–536.
6. Warnaby CE, Sleigh JW, Hight D, et al. Investigation of slow-wave activity saturation during surgical anesthesia reveals a signature of neural inertia in humans. *Anesthesiology*. 2017;127:645–657.
7. Sepúlveda PO, Carrasco E, Tapia LF, et al. Evidence of hysteresis in propofol pharmacodynamics. *Anaesthesia*. 2018;73:40–48.
8. Colin PJ, Kuizenga MH, Vereecke HEM, et al. Pharmacokinetic pharmacodynamic perspective on the detection of signs of neural inertia in humans. *Anesthesiology*. 2018;129:373–375.
9. Yew WS, Chong SY, Tan KH, et al. The effects of intravenous lidocaine on pain during injection of medium- and long-chain triglyceride propofol emulsions. *Anesth Analg*. 2005;100:1693–1695.
10. Memiş D, Turan A, Karamanlioğlu B, et al. The prevention of pain from injection of rocuronium by ondansetron, lidocaine, tramadol, and fentanyl. *Anesth Analg*. 2002;94:1517–1520; table of contents.
11. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the observer's assessment of alertness/sedation scale: study with intravenous midazolam. *J Clin Psychopharmacol*. 1990;10:244–251.
12. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. *Anesthesiology*. 1999;90:1502–1516.
13. Shafer SL, Varvel JR, Aziz N, et al. Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. *Anesthesiology*. 1990;73:1091–1102.
14. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. *Anesthesiology*. 1997;86:24–33.
15. Nunes CS, Ferreira DA, Antunes L, et al. Individual effect-site concentrations of propofol at return of consciousness are related to the concentrations at loss of consciousness and age in neurosurgical patients. *J Clin Anesth*. 2009;21:3–8.
16. Sun Y, Chen J, Pruckmayr G, et al. High throughput modular chambers for rapid evaluation of anesthetic sensitivity. *BMC Anesthesiol*. 2006;6:13.
17. Glen JB, White M. A comparison of the predictive performance of three pharmacokinetic models for propofol using measured values obtained during target-controlled infusion. *Anaesthesia*. 2014;69:550–557.
18. Glen JB, Servin F. Evaluation of the predictive performance of four pharmacokinetic models for propofol. *Br J Anaesth*. 2009;102:626–632.
19. Masui K, Upton RN, Doufas AG, et al. The performance of compartmental and physiologically based recirculatory pharmacokinetic models for propofol: A comparison using bolus, continuous, and target-controlled infusion data. *Anesth Analg*. 2010;111:368–379.
20. Lang E, Kapila A, Shlugman D, et al. Reduction of isoflurane minimal alveolar concentration by remifentanil. *Anesthesiology*. 1996;85: 721–728.
21. Westmoreland CL, Sebel PS, Gropper A. Fentanyl or alfentanil decreases the minimum alveolar anesthetic concentration of isoflurane in surgical patients. *Anesth Analg*. 1994;78:23–28.

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