

Effects of Sevoflurane and Propofol on the Nociceptive Withdrawal Reflex and on the H Reflex

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Background: The predominant target of anesthetics to suppress movement responses to noxious stimuli is located in the spinal cord. Although volatile anesthetics appear to produce immobility by actions on the ventral rather than the dorsal horn, the site of action of propofol remains unclear.

Methods: In a crossover design, the authors compared in 13 volunteers the effects of sevoflurane and propofol on the amplitudes of the H reflex, which is mediated exclusively in the ventral horn and a withdrawal reflex (RIII Reflex), which integrates dorsal and ventral horn function. The concentrations were adjusted according to a Dixon up-and-down approach, depending on movement responses to tetanic stimulation.

Results: Sevoflurane and propofol concentrations ranged from 1.2 to 1.6 Vol% and 3 to 6 mg/l, respectively. Sevoflurane reduced the H reflex amplitude significantly to $66 \pm 17\%$ (mean \pm SD) of its control values. Propofol did not significantly reduce the H reflex. The reductions under the two drugs differed significantly. The RIII reflex amplitude was significantly reduced to $19 \pm 10\%$ and $27 \pm 12\%$ (mean \pm SD) of the control values by sevoflurane and propofol, respectively. The reductions did not differ between the drugs.

Conclusions: Probably because of the polysynaptic relay, the attenuation of the withdrawal reflex exceeds the attenuation of the H reflex. Sevoflurane produces a larger inhibitory effect on the H reflex than propofol, which confirms that the ventral horn is a more important target for volatile anesthetics, whereas effects of propofol on this site of action are rather limited. Our findings indirectly suggest for propofol a relatively stronger effect within the dorsal horn.

VOLATILE anesthetics suppress movement in response to noxious stimuli, primarily by their direct action on the spinal cord.¹ Mounting evidence from animal studies suggests that their predominant site of action within the spinal cord is the ventral rather than the dorsal horn.^{2,3}

The spinal mechanisms by which propofol suppresses movement on noxious stimuli remain rather unclear.

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Animal studies in rats have shown that propofol, just like halothane and isoflurane, depresses responses to noxious mechanical stimulation primarily in the ventral horn, whereas the suppression of such responses in the dorsal horn remains negligible.⁴ These findings differ from an earlier report in other species,⁵ which indicated that propofol has a direct depressant effect on dorsal horn neuronal responses to noxious stimulation in goats.

The aim of this study was to compare the targets of both propofol and sevoflurane within the human spinal cord that might contribute to the suppression of movement. We employed two reflex circuits including neurons located in different parts of the spinal cord: the proprioceptive H reflex, including only ventral horn neurons, and the RIII reflex as a component of the nociceptive flexion reflex, which includes ventral as well as dorsal horn neurons.

The H reflex arc consists of the Ia afferents, the spinal motoneurons, and the corresponding muscle fibers, and it can be regarded as an analogue of the mechanically induced stretch reflex. Physiologically, the synaptic transmission between the Ia afferent and the motoneuron is modulated presynaptically and postsynaptically by numerous interneurons located in the ventral horn. Changes in the H reflex amplitude faithfully reflect the net modulation of excitatory and inhibitory influences on the reflex arc within the ventral horn.

The nociceptive flexion reflex is a polysynaptic spinal withdrawal reflex that has been widely used in pathophysiological and pharmacological studies to provide information on human nociceptive pathways. The reflex arc is mediated by a complex network of interneurons at spinal level,⁶⁻⁹ including the wide dynamic range neurons and multireceptive neurons located in lamina V of the dorsal horn of the spinal cord.¹⁰⁻¹³ The nociceptive flexion reflex consists of an early response (RII reflex) and a late response (RIII reflex). Although the RII reflex is a nonnociceptive A- β fiber-mediated response, the RIII reflex is a high-threshold nociceptive A- δ fiber-mediated reflex.¹⁴⁻¹⁷ The RIII reflex response is recorded electromyographically over the biceps femoris muscle after the application of electrocutaneous stimuli to the ipsilateral sural nerve.

We also used repetitive stimulation of the RIII reflex at a frequency of 2 Hz, which has been shown to be an appropriate tool to evaluate temporal summation.¹⁸⁻²⁰ The reduction of temporal summation has been related to immobility induced by volatile anesthetics,²¹ and it depends on N-methyl-D-aspartic acid receptors.

In the current study, we recorded H reflex recruitment curves as well as RIII reflex recruitment curves during both single and repetitive stimulation at concentrations

Table 1. Characteristics of the 14 Subjects Included in the Study

Subject	Age, years	Weight, kg	Height, cm	Sevoflurane			Propofol				
				Concentration, Vol%	Movement, +/-	Consecutive Order	Calculated Plasma Concentration ($\mu\text{g/ml}$)	Measured Plasma Concentration ($\mu\text{g/ml}$)	Movement, +/-	Consecutive Order	
A	21	85	176	1.6	-	1	3.75	2.86	+	4	
B	29	68	174	1.2	+	11	3.75	5.45	-	13	
C	27	84	184	1.4	+	12	3.75	3.18	+	6	
D	22	64	182	1.4	-	2	4.5	6.43	-	7	
E	25	68	178	1.2	+	3		Dropout			
F	23	70	175	1.4	-	4	4.5	4.90	-	3	
G	24	60	174	1.2	+	5	3.75	5.86	-	8	
H	22	75	187	1.4	+	6	5.25	6.67	-	11	
I	23	80	187	1.6	-	7	4.5	4.18	-	5	
J	21	78	180	1.6	Not evaluated	13	4.5	4.52	-	12	
K	22	83	192	1.6	-	9	4.5	6.65	+	1	
L	22	70	170	1.4	-	10	6	6.25	-	2	
M	28	83	186	1.4	+	8	3	3.34	+	9	
N	27	70	176	1.6	+	14	4.5	4.41	+	10	

of sevoflurane and propofol that suppressed movement responses to tetanic electrical stimulation. Comparing the effects of propofol and sevoflurane on the two different reflexes could allow differentiating their site and mechanism of action within the intact spinal cord.

Materials and Methods

Subjects

After approval of the local ethics committee (Ethikkommission des Landes Berlin) and the German federal institution for drugs and medical devices (BfArM), the study was conducted in 14 healthy male volunteers. Their demographic data are presented in table 1. All participants were carefully briefed concerning the experimental procedures and gave informed written consent.

Anesthetic Procedure

The study was performed in an operating or induction room with anesthesia and emergency equipment. The experimental sessions were all conducted at the same hour in the afternoon to exclude the possible influence of circadian rhythms on the RIII reflex.²²

During the entire study period, subjects were comfortably rested in therapy beds with a flexed leg-section to maintain angles of 120 degrees in the hip and 130 degrees in the knee. An adjustable orthopedic splint that prevented movement in the knee-joint in addition secured the right leg, where the H reflex was elicited. The volunteers were scheduled for propofol or sevoflurane in random order.

Before the study period, standard monitoring, including noninvasive blood pressure, electrocardiography, pulse oximetry, a tight-fitting facemask for measuring end-tidal carbon dioxide, surface-electrodes for the bispectral index (BIS; Aspect Medical Systems Newton, MA) and an intravenous access *via* a forearm vein were established. The subjects fasted at least 6 h before the administration of the anesthetics.

Propofol was infused intravenously *via* a target-controlled infusion pump (Base primea; Fresenius, Bezins, France) programmed using the weight- and age-corrected pharmacokinetic parameter set of Schnider.²³ Sevoflurane was administered using an anesthesia work station (Primus or Zeuss; Dräger Medical, Lübeck, Germany) *via* the facemask. End tidal drug concentrations were measured continuously using the build-in infrared spectrophotometer of the anesthesia monitor (iMM Anesthesia Monitor; Datex Ohmeda S/5 FM, Helsinki, Finland). To accelerate the distribution of sevoflurane, higher concentrations than the target level were administered during the first 5 min.

To avoid hypoventilation under higher concentrations of propofol or of sevoflurane, the airway was maintained with chin lift, jaw thrust, or a Guedel tube if needed clinically. A laryngeal mask was placed in some subjects when ventilation problems persisted. All subjects breathed spontaneously throughout the study. End tidal carbon dioxide concentration remained constant by assisting ventilation manually, if necessary.

All measurements during drug administration were performed under steady-state conditions (*i.e.*, before measurements commenced), and the end tidal concentration of sevoflurane or the target level of the target-controlled infusion was kept constant for at least 30 min at a value predetermined by the Dixon up-down method.²⁴ The starting values for the up and down method were 1.6 Vol% and 4.5 mg/l for sevoflurane and propofol, respectively. The concentrations of every following subject were increased or decreased by 0.2 Vol% sevoflurane or 0.75 mg/l (1.5 mg/l for the first two subjects) for propofol, depending on whether the previous subject receiving the same drug did or did not move in response to a noxious stimulus. The noxious stimulus was a tetanic electric stimulus of 30 s (70 mA and 50 Hz) applied *via* a peripheral nerve stimulator to surface electrodes placed on the ulnar side of the forearm. It was applied

approximately 2 h after the induction of anesthesia when all the reflex recordings were completed. Only movements of the head or extremities excluding the stimulated arm were considered positive. Immediately after the tetanic stimulation, venous blood samples were drawn from the arm on the side contralateral to the side used for propofol administration.

Blood samples were kept at 5°C until centrifugation within 2 h. After separation, plasma samples were stored at -18°C until extraction with acetonitril and analysis within 12 weeks. Plasma propofol concentrations were determined in analogy to the method described by Pavan *et al.*²⁵ using high-performance liquid chromatography with fluorescence detection at 219 nm (LC-6A, SPD10avp, and RP-8rc; Shimadzu, Kyoto, Japan). For each batch of blood samples, a standard curve was computed by adding pure propofol liquid to drug-free plasma to achieve concentrations of 0, 0.1, 0.25, 1.0, 2.5, and 10.0 mg/l.

H Reflex

The underlying circuitry of the H reflex and exemplary recordings are shown as supplemental digital content (See figure 1a and b, Supplemental Digital Content 1, <http://links.lww.com/A1210>). The H reflex was elicited every 12 s with a rectangular pulse of 1 ms duration (Digitimer DS7A; Digitimer Ltd, Welwyn Garden City, United Kingdom) by stimulation of the right tibial nerve with the cathode (gold-plated half-ball electrode, diameter 7.5 mm) in the popliteal fossa and the anode placed just above the patella. Reflex responses were recorded with paired adhesive Ag/AgCl-electrodes (Medicotest "blue point," Istrykke, Denmark) placed over the soleus muscle with an interelectrode distance of 2 cm. The electromyographic response was amplified 500-fold (Neuropack 4 mini; Nihon Kohden, Tokyo, Japan), digitized with a sampling rate of 5 kHz (Mikro 1401 mk II; CED Ltd. Cambridge, England), and stored on a mobile computer hard disk for further analysis. The peak-to-peak amplitude of the H reflex and M-wave (direct muscle response due to motor fiber stimulation in the tibial nerve) was measured online using Signal 3.01 (CED Ltd.).

The intensity of the stimulating pulses was increased in eight to ten steps from below the threshold of the H reflex to beyond the currents that were needed to obtain a maximal H reflex response (see figure 1c, Supplemental Digital Content 1, <http://links.lww.com/A1210>). At least three of these sequences were performed during two states: before and during drug administration.

To reduce interindividual variability, the H reflex amplitude was normalized to the direct maximal muscle response (M_{\max}) of the soleus muscle after a supramaximal (greater than 60 mA) stimulation of the tibial nerve. M_{\max} was determined before and after the H reflex measurement cycles during control conditions and under drug administration. Statistical analysis is based on

the average ratio of H_{\max} to M_{\max} , which is the most conventionally used parameter of motor excitability.²⁶

Stimulus intensity was normalized to the stimulus intensity at the threshold of the M-response. The motor threshold was defined as the lowest stimulus intensity producing an amplitude in the M-wave time window that differed significantly from that of the static noise in three measurements. After normalizing the recruitment curves for every single subject, an average curve of all subjects was calculated for each state by assuming linear progressions between every two points of the measured recruitment curves.

RIII Reflex Recording Procedure

Single Stimulation. To elicit the RIII reflex of the left biceps femoris muscle, the left sural nerve was stimulated at its retromalleolar pathway *via* surface electrodes (interelectrode distance: 30 mm). Stimuli were applied every 12 s, with each stimulation trial consisting of a train of 5 rectangular electrical pulses of 1 ms duration each, at 200 Hz (DS7A; Digitimer Ltd, Hertfordshire, England). This train of five pulses is perceived as a single twitch and therefore called *single stimulus*. To record the reflex response, surface electrodes were placed over its lateral tendon and over the biceps femoris muscle itself, 10 cm proximal of the popliteal fossa (fig. 1a). The signals were amplified 5000-fold (Neuropac Mini; Nihon Kodan, Tokyo, Japan), digitized at a sampling rate of 5 kHz (Mikro 1401 mk II; CED Ltd.) and analyzed using Signal 3.10 (CED Ltd.). The original tracings (fig. 1b) of the withdrawal reflex response were visualized on a mobile computer screen and stored on a hard disk. The RIII reflex amplitude was calculated as the peak-to-peak amplitude of the withdrawal reflex response within the time window of 90–180 ms after the onset of the stimuli. This time restriction avoids contamination by tactile (RII) responses that occur between 50 and 70 ms and by artifacts produced by involuntary movements that occur as early as 250 ms after the stimulus.

Complete recruitment curves for the reflex as a function of the stimulation current were established by increasing the stimulation current from below the threshold in steps of 1 to 2 mA (depending on the slope of the recruitment curve after cursory analysis of the first five stimulations) up to the tolerance threshold (fig. 1c). In healthy subjects, the increment of the stimulation intensity above the reflex threshold leads to a linear increase of the reflex amplitude and subjective pain perception until a plateau of the RIII-amplitude is reached. At very high stimulation intensities, around the tolerance level, a further increase does not result in higher amplitudes of the reflex.²⁷ Three recruitment curves have been recorded during control conditions and drug administration, respectively. To visualize the drug effect on the different stimulation intensities, an average curve of all subjects was calculated for each state (control and drug)

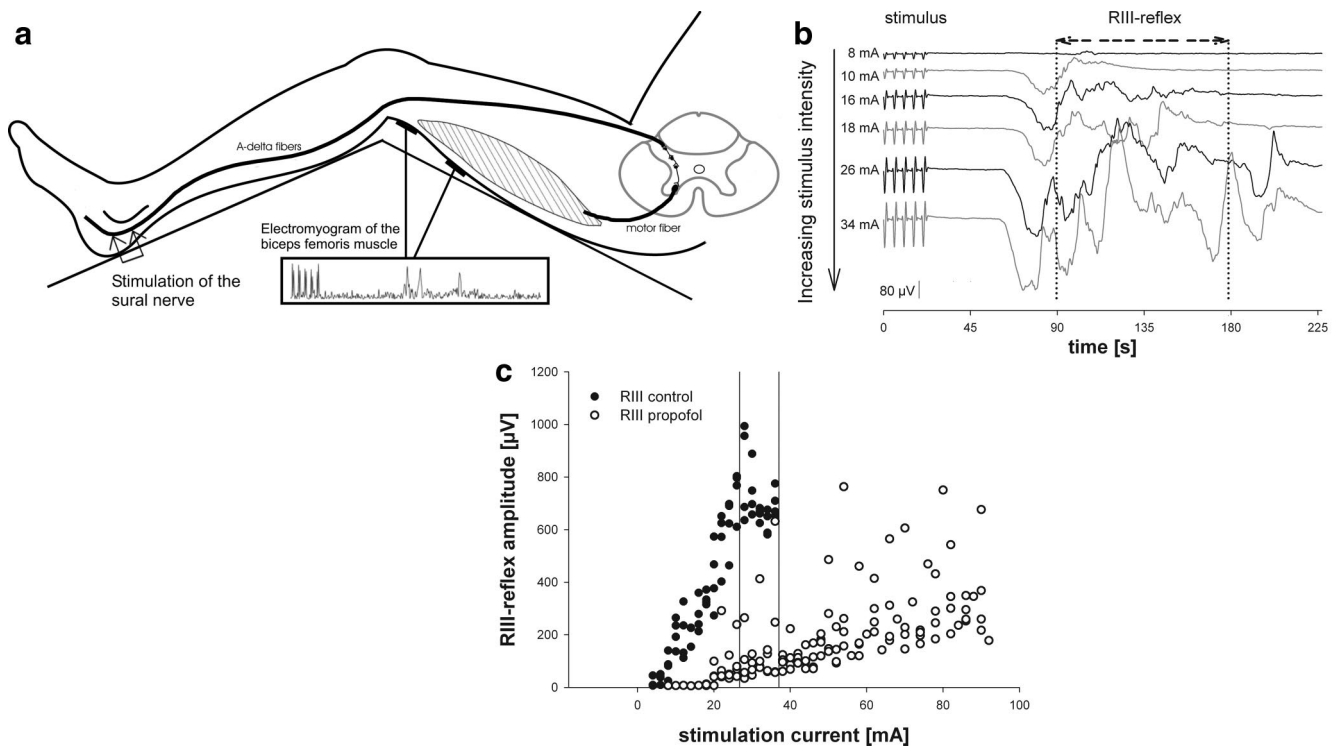


Fig. 1. (a) Experimental setting of the RIII reflex recording. The RIII reflex is elicited by electrical stimulation of the sural nerve at its retromalleolar pathway *via* surface electrodes with an interelectrode distance of 30 mm. To record the RIII reflex, the electromyogram of the ipsilateral biceps femoris muscle is monitored *via* surface electrodes over its lateral tendon and over the muscle itself 10 cm proximal of the popliteal fossa. (b) Sample recordings of the RIII reflex at different stimulus intensities under control conditions. The amplitudes of the reflex responses in the interval 90–180 ms after the stimulus were analyzed. (c) RIII recruitment curve during control conditions and propofol administration. The amplitudes of the RIII reflex are plotted *versus* the stimulation current. The stimulation current was increased in steps of 1 to 2 mA. The increment of the stimulation intensity above the reflex threshold leads to a linear increase of the reflex amplitude and subjective pain perception until a plateau of the RIII-amplitude is reached. At very high stimulation intensities, around the tolerance level, a further increase does not result in higher amplitudes of the reflex. At least three registrations of the recruitment curve were performed during control conditions and drug administration. Only those RIII reflex responses that were recorded within the range of the five highest stimulation intensities (*i.e.*, close to tolerance level) during control conditions were included in the statistical analysis. The area between the vertical lines contains all values that were included in the statistical analysis. Three recruitment curves have been recorded during control conditions and drug administration, respectively.

by assuming linear progressions between every two points of the individual recruitment curves. Therefore the stimulation current was normalized to the RIII reflex threshold under control conditions, which was defined as the minimal current that resulted in five consecutive reflex responses that differed significantly from baseline noise (visual control). The threshold current was identified before RIII reflex measurements commenced.

Repetitive Stimulation of the RIII Reflex. Stimulation sites and recording procedures remained unchanged for the repetitive stimulation, which was only performed during anesthesia.²⁸ The wind-up ratio, defined as the maximal Reflex amplitude of the third, fourth, or fifth stimulus divided by the RIII amplitude after the first stimulus, was calculated offline for each multiple stimulation. Therefore, the RIII amplitude of the first stimulus had to differ significantly from the baseline noise, which was verified by visual control of the original tracings. An exemplary tracing of the multiple stimulation is presented in figure 2 of the supplemental

digital content (See figure, Supplemental Digital Content 2, <http://links.lww.com/A1211>).

Data Analysis and Statistics. For statistical analysis of the RIII reflex, we compared the individual mean RIII reflex amplitudes during control states and under drug influence. During the control conditions, the reflex responses to the five highest stimulation currents that could be applied limited by pain tolerance were used for analysis. During the drug conditions, the same stimulation intensities were applied, and the reflex responses were compared with the control condition values using repeated measures ANOVAs. For statistical analysis of the H reflex, we compared the individual mean H_{\max}/M_{\max} during control conditions with the individual mean H_{\max}/M_{\max} during drug administration by using repeated measures ANOVAs.

We also used repeated measures ANOVAs with Bonferroni posttest to compare the individual mean values of bispectral index, heart rate, mean noninvasive blood pressure, and oxygen saturation between drugs and states (before and during drug administration). To calculate the

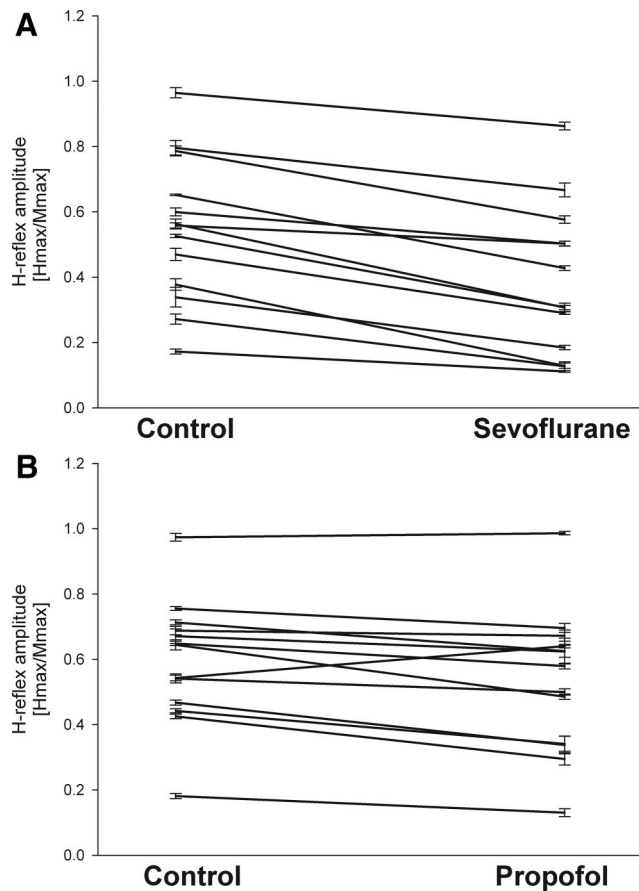


Fig. 2. Suppression of maximum H reflex amplitude normalized to maximum M wave amplitude (H_{max}/M_{max}) by sevoflurane (A) and propofol (B). Mean H_{max}/M_{max} ratios of all subjects are shown for the sevoflurane group and propofol group. The error bars represent the SEM. Lines link data points of identical individuals.

individual mean value for each of the four different parameters, we included only those values that were obtained during the H reflex measurement (before and during drug administration). In doing so, we avoided possible interference with the nociceptive stimulation of the RIII reflex.

A paired *t* test was used to compare the effect of sevoflurane *versus* propofol on the mean individual wind-up ratios obtained during multiple RIII reflex stimulation.

In both statistical tests, $P < 0.05$ was chosen to indicate statistical significance. Data in the text are given as mean \pm SD.

A logistic regression model was used to determine the EC_{50} value for the loss of movement response to a noxious electrical stimulus (SigmaPlot for Windows 2001 Version 7.0; Systat Software, Inc. Chicago, IL).

Results

Thirteen volunteers completed the study and received both drugs (table 1). One subject (J) began to cough, probably as a result of saliva aspiration during sevoflurane administration after the H reflex measurements during drug

Table 2. Mean Values and SD of Heart Rate (HR), Mean Blood Pressure ($NIBP_{mean}$), and Bispectral Index (BIS)

	HR	$NIBP_{mean}$	BIS
Propofol control	64.4 \pm 10.7†	92.8 \pm 6.7†	93.5 \pm 7.6†
Sevoflurane control	62.9 \pm 12.5	95.4 \pm 8.4†	96.2 \pm 1.8†
Propofol	70 \pm 10.3*†	77.2 \pm 8.3†	30.8 \pm 8.7*†
Sevoflurane	60.5 \pm 10.9*	80 \pm 5.3†	47.5 \pm 5.7*†

To exclude effects from nociceptive stimulation on those parameters, the values are only based on the data collected during H reflex recordings before and during drug administration. Statistics: repeated measures ANOVA, Bonferroni's multiple Comparison Test.

* Significant difference between the drugs within the corresponding time of measurement (control and anesthesia); † significant difference between control and anesthesia within the corresponding drug group.

administration were already completed. The study on this subject was discontinued after the subject received a bolus of propofol to facilitate ventilation *via* the laryngeal mask. Only the H reflex but not the RIII reflex data of this subject could be included in the study. One other volunteer (E) refused propofol administration after he had completed sevoflurane measurements. His refusal had been expressed after the next volunteer for sevoflurane was already included. Therefore, the up-and-down method for sevoflurane was continued as if this subject participated in the study but the collected data during sevoflurane administration was not included in the statistical analysis.

For sevoflurane and propofol, we recorded seven cross-over observations within the up-and-down method. The sevoflurane and calculated propofol concentrations ranged from 1.2 to 1.6 Vol% and 3.0 to 6 mg/l, with median values of 1.4 Vol% and 4.5 mg/l, respectively. By using logistic regression analysis an $EC_{50tenaus}$ of 4.10 ± 0.83 μ g/ml (plasma concentration) and 1.42 ± 0.20 Vol% can be calculated for propofol and sevoflurane, respectively.

No relevant changes in arterial oxygen saturation or end tidal carbon dioxide concentration were observed throughout the study. Control values of mean arterial blood pressure, heart rate, and bispectral index that were collected during H reflex measurement did not differ significantly between the two groups (table 2). Bispectral index values were significantly reduced by both drugs and were significantly lower during propofol than during sevoflurane administration (repeated measures ANOVA with Bonferroni multi-comparison $P < 0.001$). The heart rate was significantly ($P < 0.05$) increased during propofol anesthesia. This increase resulted in significant difference of the heart rate during propofol administration in comparison to sevoflurane administration ($P < 0.001$). Both anesthetics reduced mean arterial blood pressure in comparison to the control values ($P < 0.001$). The amount of reduction did not differ between both groups during drug administration.

Suppression of the H Reflex

Mean values of the maximum H reflex amplitude normalized to the maximum M wave amplitude ($H_{max}/$

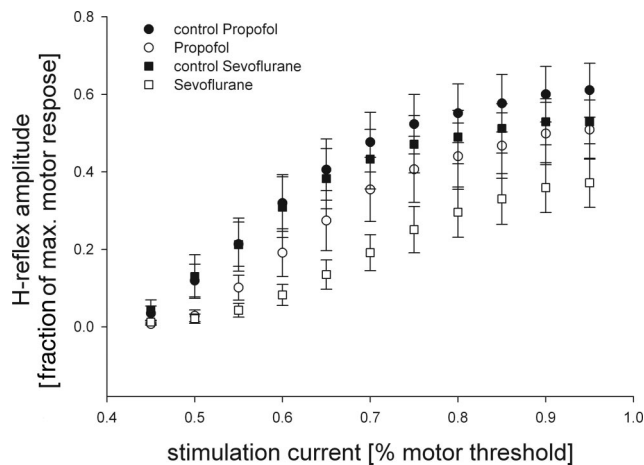


Fig. 3. Suppression of H reflex recruitment curves by sevoflurane (circles) and propofol (squares). The ascending part of the averaged H reflex recruitment curves of all 13 subjects before (filled symbols) and during (open symbols) drug administration is presented. The H reflex amplitude is normalized to the individual M_{max} (maximal motor response to electrical stimulation of the tibial nerve) of each corresponding measurement. The stimulation current is normalized to the motor threshold of the M wave. Error bars represent the SEM.

M_{max}) for each individual before and during drug administration are presented in figure 2. The reduction of the H_{max}/M_{max} ratio averaged $66 \pm 17\%$ and $87 \pm 14\%$ of the control values during sevoflurane and propofol administration, respectively. However, this reduction was statistically significant only during sevoflurane administration (repeated measures ANOVA with Bonferroni multi-comparison test $P < 0.001$). The comparison of the H_{max}/M_{max} ratio during drug administration between both groups reveals a stronger attenuation of sevoflurane than of propofol ($P < 0.001$), whereas the control mean \pm SD values (propofol 0.59 ± 0.19 ; sevoflurane 0.54 ± 0.23) did not differ significantly ($P > 0.05$).

The averaged H reflex recruitment curves for the states before and during drug administration presented in figure 3 show that the stronger attenuation of the H reflex during sevoflurane administration is not limited to the maximum H reflex amplitude, but it is present within the entire ascending part of the recruitment curve.

Suppression of the RIII Reflex

Individual mean values of the RIII reflex amplitude of the highest five stimulation intensities that could be recorded before drug administration and the corresponding values during drug administration are presented in figure 4.

The repeated measures ANOVA reveals significant differences of drug versus control values (Bonferroni multi-comparison test, $P < 0.01$) that amount to an average reduction of $19 \pm 10\%$ and $27 \pm 12\%$ of the control values for sevoflurane and propofol, respectively. Neither the control values nor the amount of reduction induced by the drug was significantly different ($P > 0.05$) in both groups.

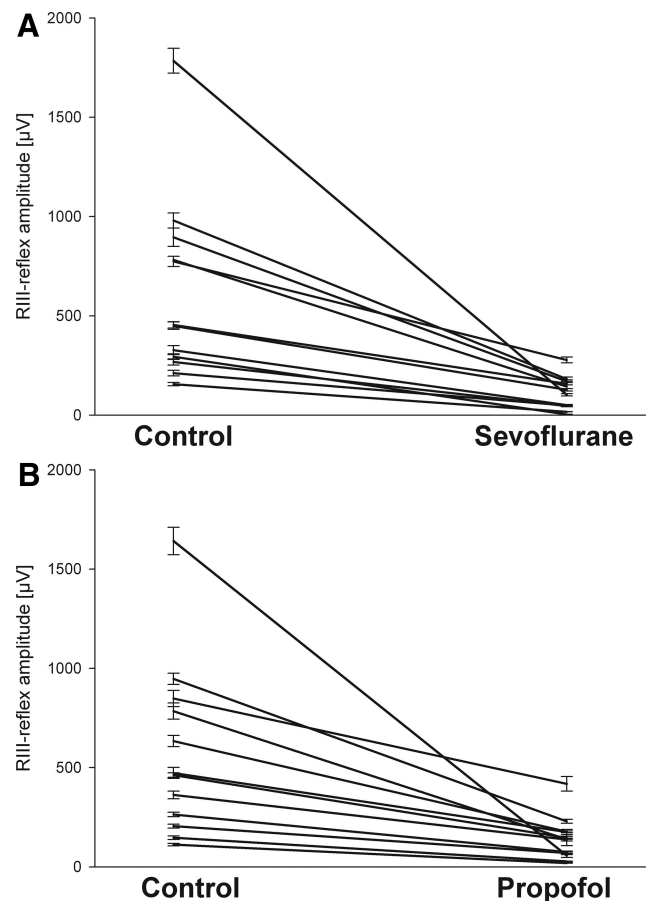


Fig. 4. Suppression of maximum RIII amplitude by sevoflurane (A) and propofol (B). Individual mean values of the RIII amplitude recorded from the five highest stimulation currents around the pain tolerance level are presented for the sevoflurane group and the propofol group. Error bars represent the SE. Lines link data of identical individuals.

The averaged RIII reflex recruitment curves are presented in figure 5. At lower stimulation currents, they display a relatively stronger attenuation of the RIII reflex amplitude during sevoflurane administration. All individual RIII reflex and H reflex recruitment curves are illustrated as supplemental digital content in figure 3 (See figure, Supplemental Digital Content 3, <http://links.lww.com/A1212>).

RIII Reflex Multiple Stimulation

The wind-up ratios that were calculated after each repeated stimulation of the RIII reflex were independent of the applied stimulation current if the first stimulus differed from baseline noise. Mean individual wind-up ratios of all subjects in both groups are presented as supplemental digital content figure 4 (See figure, Supplemental Digital Content 4, <http://links.lww.com/A1213>). The paired t test did not reveal significant differences between sevoflurane and propofol administration ($P > 0.05$).

Discussion

Both H reflex^{29,30} and nociceptive withdrawal reflexes³¹ are reduced dose-dependently by propofol and sevoflu-

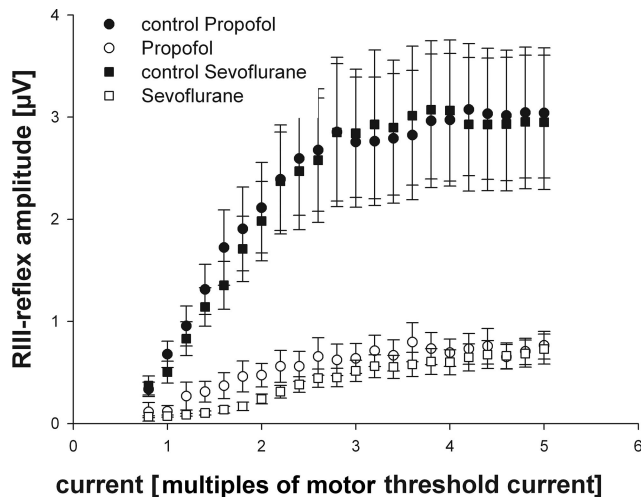


Fig. 5. Suppression of averaged recruitment curves of the RIII reflex after single stimulation by sevoflurane (circles) and propofol (squares). The averaged RIII reflex recruitment curve of all 12 subjects before (filled symbols) and during (open symbols) drug administration is presented. The stimulation intensity is normalized to the threshold current of the RIII reflex under control conditions. Error bars represent the SEM.

rane in humans. However, this is the first study in which the effects of two classes of anesthetics have been compared simultaneously on the monosynaptic H reflex and a nociceptive flexor reflex *in vivo* at concentrations that suppress movement responses to noxious stimuli. We have shown a striking difference of the degree to which both reflexes are reduced by the two anesthetics. The relative reduction of the polysynaptic RIII reflex amplitude was more than four times higher than that of the H reflex. This difference can probably be attributed to the higher number of neurons interposed in the RIII reflex pathway in comparison to the H reflex.

Our experimental setup might allow for distinguishing between preferential targets of the respective drugs within the spinal cord that might contribute to surgical immobility. Reduction of the H reflex amplitude could be the result of at least three mechanisms that are all exclusively mediated within the ventral horn: (1) a reduction of the motoneuronal excitability due to changes of excitatory and inhibitory postsynaptic influences; (2) reduction in the amount of neurotransmitter released by the Ia afferent terminals; (3) a variation of intrinsic motoneuron membrane properties.

The nociceptive flexion reflex circuitry integrates a central processing site of sensory information in the dorsal horn of the spinal cord and a central processing site for motor output in the *ventral horn*^{32,33}; therefore, its reduction is mediated by drug effects on either one or both of these sites. The results of this study demonstrate a stronger reduction of the H reflex by sevoflurane than by propofol, whereas both drugs suppress the nociceptive flexion reflex to a comparable degree. The more profound H reflex reduction by sevoflurane directly indicates that sevoflurane has stronger suppressive effects on ventral horn excitability

than propofol, at least in the concentration range we used. In this context, the similar suppression of the nociceptive flexion reflex indirectly implies that propofol would have comparably stronger effects on the dorsal horn.

These results are consistent with those that have been described by Matute *et al.*, who have investigated the effects of propofol (1 μM) and sevoflurane on monosynaptic and on polysynaptic nociceptive reflexes in hemisectioned spinal cord preparations of newborn rats. Sevoflurane (250 μM) almost abolished action potentials firing evoked by repetitive activation of nociceptive afferents, whereas propofol (1 μM) only produced a reduction close to 50% of the control values.³⁴ Monosynaptic reflexes were largely depressed at the aforementioned concentrations by sevoflurane, whereas propofol was ineffective.

The fact that monosynaptic reflexes were not attenuated by propofol *in vitro* but lightly in our study *in vivo* raises the question of the extent to which propofol effects on ventral horn excitability are really direct effects at the spinal level or rather a consequence of enhanced inhibitory input from supraspinal projections. A recent investigation,³⁵ in which motoneuronal excitability was assessed by F-waves, might support the view of indirect effects of propofol. During propofol sedation, the F-waves were suppressed, but this effect was completely reversible when consciousness was regained after mild stimulation, suggesting that motoneuron excitability is determined by the level of consciousness, rather than by propofol plasma concentration. Also, physiologic changes of the state of awareness such as rapid eye movement sleep produce a suppression of the H reflex amplitude.³⁶ Interestingly, our data also demonstrate that far lower bispectral index values are necessary to achieve immobility to noxious stimuli during propofol anesthesia than during sevoflurane anesthesia. However, the question of whether immobility and the suppression of the reflex responses are causally related to the deeper level of hypnosis during propofol anesthesia cannot be answered by our data.

Previous studies^{37,38} have shown that propofol in comparison to sevoflurane has more pronounced presynaptic inhibitory effects on Ia afferents, the afferent branch of the H reflex arc. Therefore, under the influence of propofol, a larger part of the H reflex amplitude reduction is attributable to presynaptic inhibitory effects rather than effects on the motoneurons themselves. Since the motoneuron represents the final element in the pathway of motor responses to noxious stimuli, reducing its excitability appears the most effective way to suppress such responses. The overall stronger impact of sevoflurane on the reduction of motoneuron excitability could be the reason for the slightly stronger attenuation of the RIII reflex responses during sevoflurane administration in this study. The more reliably recorded evoked potentials during propofol anesthesia in comparison to sevoflurane anesthesia³⁹ might result from a comparably facilitated activation of motoneurons during propofol administration.

In a previous study in which we recorded H reflex recruitment curves at lower concentrations of propofol (2 $\mu\text{g}/\text{ml}$) and sevoflurane (0.8 Vol), we observed comparable suppressions of the $H_{\text{max}}/M_{\text{max}}$ ratio in those subjects that received both drugs (15% for propofol and 30%) as in this study. We used higher concentrations; therefore, we would have expected a higher suppression in the current study. Besides high interindividual variability of $H_{\text{max}}/M_{\text{max}}$ ratios observed here and in other studies,⁴⁰ a possible explanation of the difference can be found in the different stimulation frequencies; the $H_{\text{max}}/M_{\text{max}}$ ratio in the current study was explored with one stimulus every 12 s, whereas stimuli were applied every 6 s in the previous study (*i.e.*, a frequency at which frequency-related depression of the H reflex resulting from homosynaptic depression is still present in normal subjects).⁴¹ This frequency-related depression occurring at stimulus intervals up to 12 s is probably related to presynaptic mechanisms at the Ia fiber-motoneuron synapse that leads to a reduced transmitter release from active Ia afferents.⁴² In awake subjects, the reduction of the interstimulus interval from 12 s to 6 s reduces the $H_{\text{max}}/M_{\text{max}}$ ratio by 25%.⁴¹ Because of its presynaptic origin, it appears possible that frequency-related depression is even greater during the administration of anesthetic drugs that might also modulate presynaptic transmitter release.

The finding that the effects of sevoflurane and propofol on temporal summation of the RIII reflex after repetitive stimulation (wind-up), which have been suggested to depend on activation of *N*-methyl-D-aspartic acid receptors,^{19,43,44} did not differ between both drugs might be surprising because volatile anesthetics, in contrast to propofol, suppress function of *N*-methyl-D-aspartic acid receptor-mediated neurotransmission *in vitro*.⁴⁵⁻⁴⁷

However, the current study is limited in its ability to address precise changes of wind-up caused by each drug because we refrained from measuring RIII wind-up during control condition.

Limitations of the Study

The present investigation is a comparative study between sevoflurane and propofol; therefore, conclusions concerning the relative contributions of ventral or dorsal horn effects of one single drug cannot be drawn from our data. Although the differences between the control values of the $H_{\text{max}}/M_{\text{max}}$ ratio did not exceed the level of significance, it is possible that the slightly higher suppression of $H_{\text{max}}/M_{\text{max}}$ ratio by sevoflurane might have some relation to the lower control values of the sevoflurane group.

The degree of drug effects on the dorsal horn cannot be assessed directly in human reflex studies such as this one. Our conclusion that propofol might act comparably stronger on the dorsal horn than sevoflurane requires that the underlying mechanisms through which both reflexes are reduced within the ventral horn are similar.

Only under this assumption would a similar suppression of the RIII reflex (integrating dorsal and ventral horn effects) by both drugs and a less effective reduction of the H reflex (parameter of ventral horn excitability) by propofol indicate stronger actions of propofol within the nociceptive sensory pathway of the RIII reflex before the motoneuron. The following theoretical considerations, however, support the assumption that the RIII reflex suppression within the ventral horn is mirrored in the reduction of the H reflex amplitude. First of all, it seems rather unlikely that anesthetic effects on the motoneuronal excitability differ between two muscles groups of the lower limb. Therefore, the reduction of motoneuronal excitability should be equally detected by changes of both H reflex and RIII reflex amplitudes. The extent to which the presynaptic drug effects on the Ia afferents differ from those on the interneurons projecting onto the motoneurons in the RIII reflex pathway remains unclear. As stated above, we only know that presynaptic effects of propofol on Ia afferents are more pronounced than those of sevoflurane,³⁸ indicating that measurement of the H reflex overestimates the reduction of motoneuron excitability by propofol in comparison to sevoflurane.³⁸

Although the H reflex is modulated by different interneuronal circuits of the ventral horn,⁴⁸ it remains possible that anesthetic effects within the ventral horn contribute to the suppression of movements that are not at all or only disproportionately represented by the change of the H reflex amplitude evaluated in this study. Recent evidence from animal studies suggests that immobilizing properties of volatile anesthetics are partly explained by preferential action on circuits generating the rhythm and shaping the pattern of the bursts of motoneurons, so called central pattern generators.^{3,49} The extent to which anesthesia-induced effects on those central pattern generators influence the H reflex is unknown; however, under physiologic conditions, the H reflex is used as a standard tool to explore the output of central pattern generators during arm movement or locomotion.⁵⁰

This study used a 30-s tetanic electrical stimulation of the ulnar nerve to determine the concentration at which movement reactions to that stimulus were suppressed in about 50% of the subjects. Although this stimulation has been reported to be an adequate experimental pain model for surgical pain during anesthesia,⁵¹ our $\text{MAC}_{\text{tetanus}}$ value (the minimum alveolar concentration that prevents movement in response to electrical tetanus stimulation in 50% of patients) for sevoflurane was 1.42, which is smaller than that of 1.84 Vol% reported for skin incision.⁵² Also, the EC_{50} value for tetanic stimulation of 4.1 $\mu\text{g}/\text{ml}$ derived from our measured propofol plasma concentration is smaller than the EC_{50} value from calculated plasma concentrations of 6.8 $\mu\text{g}/\text{ml}$ for skin incision reported by Stuart *et al.*⁵³ and it is far below that of 10 $\mu\text{g}/\text{ml}$ by Kazama *et al.*⁵⁴ Therefore, we cannot exclude that the differences in H reflex reduction between sevoflurane and

propofol might have been less pronounced at higher concentrations that would suppress movement responses to skin incision. The absolute strength and quality of the nociceptive stimulus to test movement responses is, however, not crucial to our findings as long as the same nociceptive stimulus is used for both drugs.

In summary, the results of this comparative reflex study demonstrate a profound attenuation of spinal nociceptive withdrawal reflexes by propofol and sevoflurane at concentrations that suppress movement responses to noxious stimuli. The reduction of the monosynaptic H reflex by both drugs is smaller and significantly stronger during sevoflurane administration compared to propofol. Taking into account that the H reflex is primarily mediated within the ventral horn, our results confirm that the ventral horn is a more important target for volatile anesthetics, whereas effects of propofol on this site of action are rather limited. Our findings indirectly suggest for propofol a relatively stronger effect within the dorsal horn.

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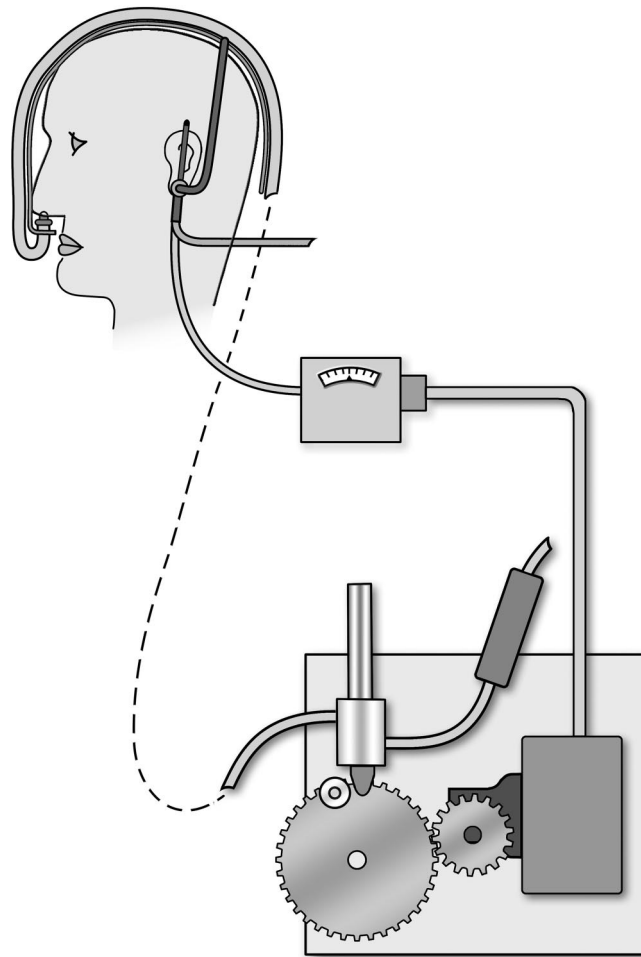
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■ ANESTHESIOLOGY REFLECTIONS

Kirschbaum's Oxygen Content Controller



An inventor of devices for providing anesthesia and for patient monitoring, Detroit obstetrician-gynecologist Harry M. Kirschbaum (1900–1959) filed a U.S. Patent application on July 2, 1942 for his “Method and apparatus for controlling the oxygen content of the blood of living animals.” His apparatus incorporated a source for transmitting light through the subject’s earlobe to register whether blood was currently “oxygenated . . . [to a] bright red color” or “darker . . . [from losing] its oxygen content.” A photo-electric cell “exposed to this beam . . . with suitable amplifying and relay means . . . is adapted to operate a valve controlling the oxygen supply” through a nosepiece. Nearly 4½ years after filing this design, Kirschbaum returned from his World War military service to find that he had been granted U.S. Patent No. 2,414,747. Although originally “designed for use by aviators,” it could also be “adapted for use by hospitals . . .” (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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