Arterial baroreflex attenuation during and after continuous propofol infusion

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The reduction of arterial blood pressure produced by propofol may be, in part, attributable to impaired baroreflex integrity. The purpose of this study was to investigate arterial baroreflex sensitivity during and after continuous propofol infusion. In urethane anaesthetized rabbits, left renal sympathetic nerves were exposed and placed on a bipolar silver electrode to record renal sympathetic nerve activity (RSNA). Mean arterial pressure (MAP) via a femoral artery and heart rate (HR) by electrocardiogram were continuously recorded. The rabbits were divided into two groups of eight each: Group 1, propofol 5 mg $\cdot kg^{-1}$ bolus followed by infusion 0.5 mg $\cdot kg^{-1} \cdot min^{-1}$; Group 2, propofol 2 mg $\cdot kg^{-1}$ bolus followed by 0.2 mg $\cdot kg^{-1} \cdot min^{-1}$. Phenylephrine pressor and sodium nitroprusside (SNP) depressor tests were carried out before propofol was started (control), at 15 and 30 min during 30 min infusion, and at 15, 30 and 60 min after its discontinuation. The change of RSNA was plotted with respect to every 5 mmHg increment and decrement of MAP to construct sympathetic baroreflex sigmoid curves, and to evaluate baroreflex sensitivity. The baroreflex sensitivity was also evaluated by calculating the ratio of maximum increase of RSNA or HR to SNP-induced maximum decrease of MAP (ΔRSNA/ΔMAP, ΔHR/ΔMAP). Despite the same decreases or increases in MAP, RSNA was attenuated after 15 and 30 min of propofol infusion in both groups compared with control ($P < 0.05$). Decreased ΔRSNA/ΔMAP gradually returned to the control level 60 min after discontinuation of propofol in Group 1. The baroreflex sensitivity for control of HR was attenuated only at 30 min in the higher propofol infusion group ($P < 0.05$). It is concluded that propofol attenuates baroreflex sensitivity for control of RSNA in a dose-dependent manner during infusion. Although recovery from anaesthesia is rapid, our data indicate that the attenuated arterial baroreflex may persist after discontinuing propofol infusion.

On attribue en partie la baisse de la pression artérielle sous propofol, à une défailiance dans le fonctionnement des baroré-cepteurs. L'étude de la sensibilité baroréflexe artérielle pendant et après une perfusion de propofol constitue l'objectif du présent travail. Chez des lapins sous anesthésie à l'uréthane, nous avons disséqué les nerfs sympathiques rénaux gauches sur lesquels on a inséré une électrode d'argent bipolaire dans le but d'étudier l'activité nerveuse sympathique rénale (ANSR). Nous avons enregistré en continu la pression artérielle moyenne (PAM) fémorale directe et la fréquence cardiaque (Fc) par électrocardiographie. Les lapins ont été repartis en deux groupes : le groupe 1 reçoit une injection de propofol 5 mg $\cdot kg^{-1}$ suivie d'une perfusion de 0,5 mg $\cdot kg^{-1} \cdot min^{-1}$; le groupe 2, une injection de propofol 2 mg $\cdot kg^{-1}$ suivie par 0,2 mg $\cdot kg^{-1} \cdot min^{-1}$. Des épreuves de vasosensibilité sont réalisés avec la phényléphrine pour la résponse vasopressive et avec le nitroprussiate de soude (SNP) pour la réponse dépressive. Ces tests sont effectués avant l'administration du propofol (contrôle), à 15 et 30 minutes pendant une perfusion de 30 minutes, et à 15, 30, et 60 minutes après l'arrêt de la perfusion. On enregistre les changements de l'ANSR en relation avec toute augmentation ou diminution par pallier de 5 mmHg de la PAM pour construire des courbes d'activité baroréflexe sympathique et en évaluer la sensibilité. La sensibilité baroréflexe est aussi évaluée par le calcul du rapport de l'accroissement maximal de l'ANSR ou de la fréquence cardiaque avec la baisse maximale de la PAM induite par le SNP. (ΔANSR/ΔPAM, ΔFc/Δ/PAM). Malgré les mêmes augmentations ou diminutions de PAM, l'ANSR montre une baisse après 15 et 30 minutes de perfusion de propofol dans les deux groupes comparés au contrôle ($P < 0,05$). La diminution du ΔANSR/ΔPAM revient rapidement aux niveaux du contrôle 60 minutes après l'arrêt du propofol dans le groupe 1. La sensibilité baroréflexe pour le contrôle de la fréquence cardiaque est atténuée seulement à la trentième minute dans le groupe où la perfusion de propofol est la plus élevée ($P < 0,05$). Nous concluons que le propofol

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diminue la sensibilité des barorécepteurs et que cette dépression est reliée à la dose pendant la perfusion. Bien que la récupération postanesthésique soit rapide, nos données montrent que cette hyposensibilité peut durer même après l'arrêt de la perfusion.

Propofol (Diprivan®, Stuart Pharmaceuticals, Wilmington, DE) is an intravenous anaesthetic drug that can be used for both induction and maintenance of anaesthesia. It possesses many desirable characteristics for an anaesthetic agent, including rapid induction and fast recovery to ambulation, with a lower incidence of nausea and vomiting than other available agents.[1-6] However, cardiovascular and respiratory depression can occur.[7-9] These include decreases in arterial blood pressure, cardiac output, systemic vascular resistance and heart rate (HR), and prolonged apnoea. It is important to be aware of these side effects of propofol, but it also is important to determine whether cardiovascular compensatory mechanisms are preserved during an infusion of propofol, even though haemodynamic conditions may be stable. The arterial baroreflex is one of the acute cardiovascular compensatory mechanisms which adjusts HR, peripheral vasoconstriction, and myocardial contractility mainly by regulating reflex sympathetic nerve activity.[10]

The aim of this study was to evaluate arterial baroreflex sensitivity during and after continuous propofol infusion using a direct measurement of renal sympathetic nerve activity (RSNA).

Methods

The study was approved by the Kansas University Institutional Animal Care and Use Committee, and appropriate guidelines for the use of animals were observed during all aspects of the study.

Fourteen New Zealand white rabbits, weighing between 2.7 and 3.2 kg, were starved overnight but had free access to water. They were anaesthetized with urethane 2.0 $g \cdot kg^{-1}$ *iv*, tracheotomized, and the lungs were ventilated mechanically with 100% oxygen, using an infant ventilator (Bourns Medical Systems, Inc., CA) at a tidal volume of 5–10 $ml \cdot kg^{-1}$ and a frequency of 20–35 $cycle \cdot min^{-1}$ to maintain $PaCO_2$ between 35 and 40 mmHg. Normothermia was maintained using a heating light and warming blanket. The rabbits were paralyzed with pancuronium bromide. (0.1 $mg \cdot kg^{-1}$ *iv*) to avoid artefacts on measurement of renal sympathetic nerve activity secondary to muscular movement.

Cannulations of the right and left ear veins were performed for administration of drugs to achieve arterial baroreflex pressor and depressor tests. Arterial blood pressure was measured directly from the femoral artery, and mean arterial blood pressure (MAP) was derived by electronic integration of the pulsatile pressure signal. The HR was calculated from lead II of the electrocardiogram, using a cardiotachometer (1321 San-ei, Japan).

TABLE I Arterial blood gas tensions before control pressor and depressor tests

	Group 1	*Group 2*
PaO_2	342.2 ± 23.5	325.9 ± 21.9
$PaCO_2$	39.9 ± 1.5	36.9 ± 2.1
pH	7.38 ± 0.12	7.40 ± 0.24

Values are mean ± SEM, $n = 7$.

The left kidney was exposed retroperitoneally by a left flank incision. Renal sympathetic nerves along the renal artery and vein were isolated using a microscope, immersed in mineral oil and placed on a bipolar silver electrode to record the renal nerve discharges. Electrical impulses recorded from the renal sympathetic nerves were amplified using a pre-amplifier (AVB 10: bandwidth: 50–3000 Hz, Nihon Kohden, Japan). The amplified nerve discharges were visualized on a dual-beam oscilloscope (VC 11 Nihon Kohden, Japan) and monitored by an audiospeaker. The neurogram was integrated by a resistance-capacitance integrator circuit (time constant 2.0 sec). Since integrated output is dependent on the voltage and frequencies of renal sympathetic nerve activity (RSNA), it was used as a measurement of overall RSNA.[11] Nerve activity was recorded after death in all rabbits as a measurement of the level of zero "noise."

After completion of surgical preparation, sufficient time (at least 30 min) was allowed for haemodynamic stabilization before the study. Control arterial baroreflex pressor and depressor tests were carried out using bolus infusions of sodium nitroprusside (SNP) 15–30 $\mu g \cdot kg^{-1}$ and phenylephrine (PHE) 5–15 $\mu g \cdot kg^{-1}$ (doses previously found to decrease or increase MAP by at least 20 mmHg). After haemodynamic stabilization, 14 animals were divided randomly into two groups: Group 1 (high-dose propofol; $n = 7$) and Group 2 (low-dose propofol; $n = 7$). Animals in Group 1 received a propofol 5 $mg \cdot kg^{-1}$ bolus injection followed by a 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ infusion for 30 min. Those in group 2 received a propofol 2 $mg \cdot kg^{-1} \cdot min^{-1}$ bolus followed by a 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$ infusion for 30 min. Arterial baroreflex pressor and depressor tests were carried out at 15 and 30 min during the infusion, and at 15, 30 and 60 min after discontinuation of the agent. Sensitivity of the arterial baroreflex was evaluated by plotting RSNA at every 5 mmHg change of MAP over 20 mmHg from the preinjection level. The RSNA was expressed as a percentage change from the resting spontaneous nerve discharge before bolus injections of SNP and PHE. Sympathetic baroreflex sensitivity also was evaluated by calculating the ratio of maximum increase of

TABLE II Change of mean arterial blood pressure, heart rate and renal sympathetic nerve activity before depressor (SNP) and pressor (PHE) tests

	SNP			*PHE*		
	Control	*Propofol (Group 1)*	*Propofol (Group 2)*	*Control*	*Propofol (Group 1)*	*Propofol (Group 2)*
MAP (mmHg)	80.8 ± 1.2	64.2 ± 4.4†	77.0 ± 1.7*	82.3 ± 3.4	66.3 ± 3.3*	76.4 ± 4.1
HR (bpm)	331.2 ± 7.1	299.1 ± 13.7	319.2 ± 5.4	333.3 ± 5.9	308 ± 9.7	328.5 ± 13.9
RSNA (%)	100 ± 0.0	87.7 ± 11.6	83.2 ± 11.7	100 ± 0.0	83.7 ± 10.8	79.7 ± 10.4

$n = 7$, $^*P < 0.05$ vs control, $\dagger P < 0.01$, MAP: mean arterial blood pressure, HR: heart rate, RSNA: renal sympathetic nerve activity.

RSNA to maximum decrease of MAP produced by SNP for the recovery period from propofol infusion (ΔRSNA/ΔMAP).[11] Similarly, the ratio of maximum increase of HR to maximum decrease of MAP produced by SNP was used in order to evaluate and compare the cardiac baroreflex sensitivity (ΔHR/ΔMAP).

All data were expressed as mean ± SE. Comparisons within the experimental protocol were made using a repeated measurement analysis of variance. Multiple comparisons between individual means were performed using the Newman-Keul method.

Results

Arterial blood gas tensions and pH values prior to control pressor and depressor tests were within physiological ranges in both groups (Table I).

The MAP decreased during both high-dose and low-dose propofol infusions at 15 min before pressor and depressor tests ($P < 0.05$) (Table II). Heart rate and resting RSNA were not decreased significantly by propofol.

There was a sigmoid relationship between RSNA and MAP by SNP-induced hypotension and PHE-induced hypertension before propofol (control) and during infusion of propofol in Group 1 (Figure 1). Despite the same MAP decreases or increases, RSNA was attenuated after 15 and 30 min of infusion compared with control ($P < 0.05$). There were no differences in attenuation of RSNA between infusions of 15 and 30 min. After discontinuance of the propofol infusion in Group 1, the decreased ΔRSNA/ΔMAP gradually returned to the control level, and at 60 min ΔRSNA/ΔMAP finally returned to the control level (Figure 2). There was a sigmoid relationship between RSNA and MAP before propofol (control) and during infusion of propofol in Group 2 (Figure 3). Although RSNA was attenuated during the low-dose propofol infusion, the degree of attenuation was less than in Group 1. The attenuated arterial baroreflex already had recovered by 15 min after discontinuance of propofol infusion in Group 2 (Figure 4). The value of ΔHR/ΔMAP during propofol infusion was lower than control only in Group 1 (high-dose propofol) and only at 30 min ($P < 0.05$) (Figure 5).

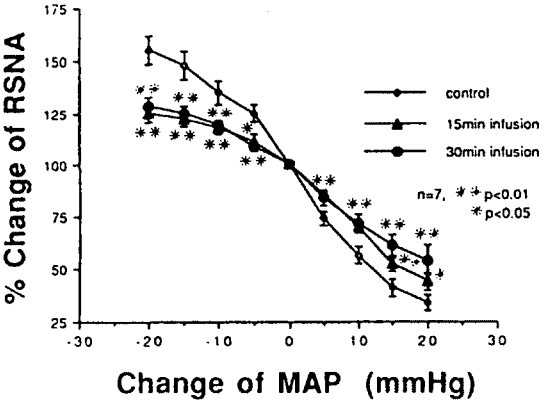

FIGURE 1 Sigmoid relationship between RSNA and MAP by SNP-induced hypotension and PHE-induced hypertension before propofol (-◇-), after 15 min (-▲-) and 30 min (-●-) infusion in Group 1. Values are mean ± SEM. $^{**}P < 0.01$, $^*P < 0.05$ vs control.

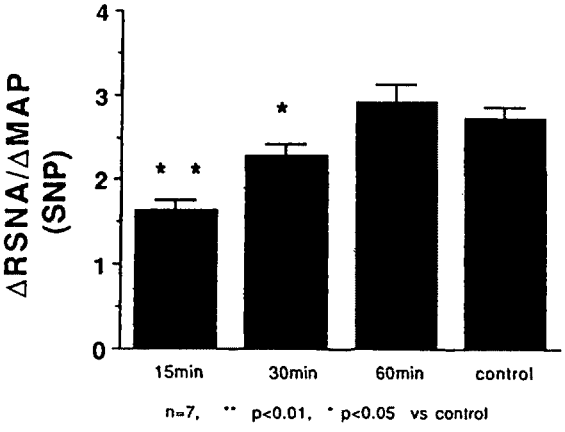

FIGURE 2 Recovery of attenuated RSNA as indicated by decreased ΔRSNA/ΔMAP during the depressor test with SNP after discontinuance of propofol infusion in Group 1. Values are mean ± SEM.

Discussion

Our data clearly indicate that the arterial baroreflex may be attenuated during propofol infusion and attenuation of the baroreflex may persist after discontinuing the infusion. This suggests that patients may develop a profound

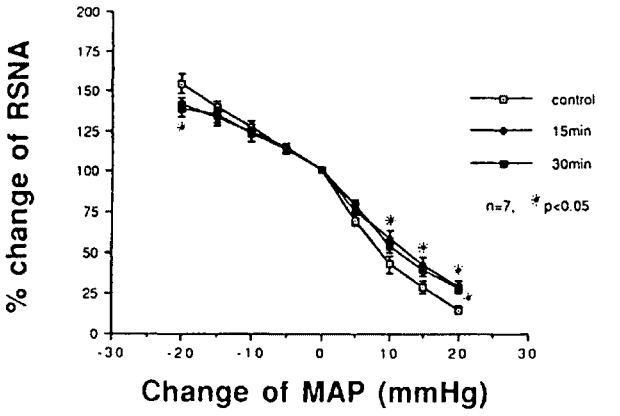

FIGURE 3 Sigmoid relationship between RSNA and MAP by SNP-induced hypotension and PHE-induced hypertension before propofol (–□–), after 15 min (–◆–) and 30 min (–■–) infusion in Group 2. Values are mean ± SEM. *$P < 0.05$ vs control.

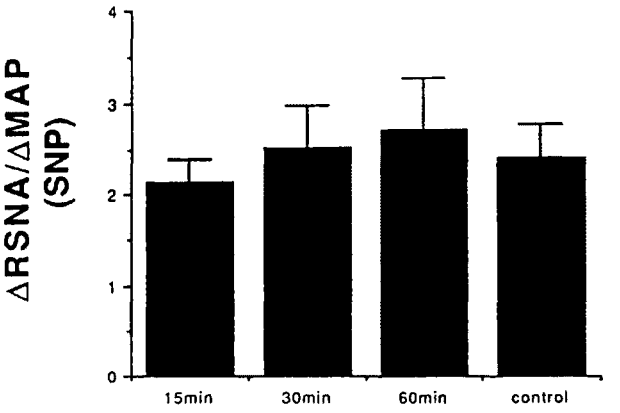

FIGURE 4 Recovery of attenuated RSNA after discontinuance of propofol infusion in Group 2. Values are mean ± SEM.

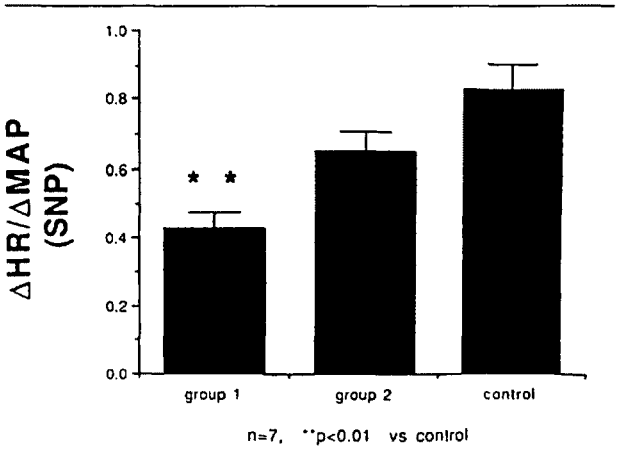

FIGURE 5 Comparison of attenuated arterial baroreflex for control of HR as indicated by the decreased ratio of ΔHR/ΔMAP between Groups 1 and 2. Values are mean ± SEM.

hypotension if acute blood loss occurs, or if a hypotensive agent is employed during propofol infusion. When infusion time is prolonged, recovery of propofol anaesthesia may be prolonged because of the long terminal elimination half-life.[1–3] This may be the main reason why baroreflex control of RSNA was still depressed 30 min after discontinuing the higher rate of propofol infusion. Gross *et al.* warned that in patients who have received propofol, return of consciousness may not ensure complete recovery of ventilatory drive.[12] Similarly, our data indicate that return of consciousness may not ensure recovery of arterial baroreflex integrity.

In our study, urethane was used for induction and maintenance of anaesthesia since it is known not to attenuate arterial baroreflex sensitivity.[13] Urethane also produces long-lasting (8–10 hr) anaesthesia, with minimal cardiovascular and respiratory depression.[14] One of the recommended clinical infusion rates of propofol is 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$ following the induction dose of 2.0 $mg \cdot kg^{-1}$.[1] In addition to this rate, we administered the drug at 2.5 times the recommended rate to achieve a dose-response study. Small animals like rabbits may require higher doses of *iv* anaesthetics than humans, and bolus doses of 5 to 7 $mg \cdot kg^{-1}$ of propofol have been recommended for animals.[14] Therefore, it is possible that the higher dose of propofol used for rabbits in this study may well be comparable to the recommended dose for humans.

To our knowledge, our study was the first to evaluate arterial baroreflex sensitivity not only during constant propofol infusions but also during recovery from propofol anaesthesia. We employed both an arterial baroreflex depressor test with sodium nitroprusside and a pressor test with phenylephrine, so that complete baroreflex sigmoid curves with RSNA changes relating to changes of MAP were constructed. Although they were reset by propofol infusions, baroreflex set points before and after 15 and 30 min of infusion were placed at the same point of zero change of MAP on the X-axis and 100% RSNA on the Y-axis in the Figures in order to compare the shape of baroreflex sigmoid curves (Figures 1, 3). The ratios of maximum increase in RSNA or HR to maximum reduction of MAP induced by sodium nitroprusside also were used to evaluate and compare the baroreflex sensitivity for control of RSNA during recovery period and HR during propofol infusion. The ratios express steepness of the baroreflex slope; the larger the ratios, the steeper the slope (more sensitive) (Figures 2, 4, 5).

During propofol infusion, HR and resting RSNA were not increased despite the reduction of MAP (Table II). When MAP is decreased, one can expect that RSNA and HR will be increased because of compensatory arterial baroreflex mechanisms. It is speculated that the depressant effects of propofol on RSNA and the central vagotonic

effect on HR[15,16] overwhelm the compensatory baroreflex mechanism to increase RSNA and HR in response to hypotension. Therefore, baroreflex set points for RSNA and HR were reset in a way to allow a decreased resting RSNA and a slower HR at the lower MAP. From this reset baroreflex set point, RSNA and HR were increased by SNP-induced hypotension and decreased by PHE-induced hypertension. It was found that the arterial baroreflex sensitivity for control of RSNA was attenuated in a dose-dependent fashion (Figures 1, 3). Our results are in agreement with the work of Ebert *et al.*, in which attenuated gain of muscular sympathetic nerve activity was reported during propofol infusion.[17] Cullen *et al.* also reported that the responsiveness of the systemic artery system to the Valsalva manoeuvre was decreased, indicating a decreased gain of systemic vascular resistance during propofol infusion.[18]

Baroreflex sensitivity of control of RSNA was attenuated even during the lower rate of propofol infusion. However, arterial baroreflex control of HR was attenuated only during the higher rate of propofol infusion at 30 min (Figure 5). This may indicate that propofol hardly attenuates baroreflex control of HR. Cullen *et al.* reported that baroreflex control of HR was not depressed by a propofol infusion.[18] Thus, degrees of attenuation on baroreflex sensitivity for control of HR and sympathetic nerve activity are quite different during propofol infusion.

In conclusion, propofol attenuates arterial baroreflex control of renal sympathetic nerve activity in a dose-dependent fashion during infusion. Although recovery from anaesthesia is rapid, the attenuated arterial baroreflex may persist after discontinuing propofol infusion.

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