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Dose-dependent effects of propofol on renal sympathetic nerve activity, blood pressure and heart rate in urethane-anesthetized rabbits

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Abstract

To evaluate the role of the autonomic nervous system in hemodynamic changes after propofol bolus injection, we used direct recordings of renal sympathetic nerve activity to examine the dose-dependent effects of propofol (2.5, 5, 10, and 20 mg/kg) on heart rate, mean blood pressure and renal sympathetic nerve activity in urethane-anesthetized rabbits. The animals were divided into four groups: animals with an intact neuraxis (intact group), cervical vagal nerve-sectioned animals (vagotomy group), carotid sinus and aortic-nerve sectioned animals (SAD group), and animals with SAD plus vagotomy (SADV group). Heart rate did not change significantly even after administration of 2.5 and 5 mg/kg but decreased markedly on 20 mg/kg injection in all groups. The intact and vagotomy groups had augmented renal sympathetic nerve activity with insignificant changes in mean blood pressure after 5 mg/kg injection of the agent. Insignificant changes of renal sympathetic nerve activity but a remarkable decrease of mean blood pressure appeared after 10 mg/kg propofol. Sustained hypotension in parallel with a profound depression of renal sympathetic nerve activity developed at the dose of 20 mg/kg. In SAD and SADV groups, however, dose-dependent depressions of renal sympathetic nerve activity were accompanied by decreases of mean blood pressure. These results suggest the following: (1) propofol-induced hypotensive effects are probably produced by the central-mediated sympathetic depression. (2) The baroreceptor reflex may be preserved at the lower dose of the agent. (3) Heart rate does not change significantly unless a large dose of propofol is used. The difference in effects on heart rate and on mean blood pressure may denote a greater inhibition of sympathetic vascular outflow than of the cardiac sympathetic outflow regulating cardiac rate and contractility. This hypothesis needs further clarification.

Keywords: Arterial baroreceptor; Autonomic nervous system; Propofol

1. Introduction

Propofol is a rapid-acting intravenous anesthetic that has been used for both induction and maintenance of general anesthesia. Systemic hypotension is a serious complication of propofol anesthesia (Sebel and Lowdon, 1989; Reves et al., 1994). The mechanism of propofol-mediated hypotension may involve sympathetic depression (Sellgren et al., 1990, 1994; Deegan et al., 1991; Ebert et al., 1992). However, responses of muscle sympathetic nerve activity in intact humans failed to reveal whether propofol-induced inhibition of nerve activity is centrally or peripherally mediated. There were also several limitations to the human research because the authors were unable to provide dose–response information (Sellgren et al., 1990, 1994; Ebert et al., 1992).

Recently, there have been reports on work with various species or experimental settings regarding propofol effects on baroreflexes, ranging from no (Cullen et al., 1987; Samain et al., 1989) to slight (Blake et al., 1988; Sellgren et al., 1992), or marked (Ebert et al., 1992; Kamijo et al., 1992; Sellgren et al., 1994) depression of baroreflex sensitivity by the agent. Effects of propofol on heart rate are also controversial, from no changes (Coates et al., 1987, Claeys et al., 1988) to decreases (Cullen et al., 1987; Brüssel et al., 1989) and even increases (Muzi et al., 1992; Wouters et al., 1995). It was reported earlier (Cullen et al., 1987; Deutschman et al., 1994) that propofol-induced bradycardia may be due to vagotonic mechanisms. Krassioukov et al. (1993, 1995) using microinjection of glycine

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in the ventrolateral medulla and pontine reticular formation, indicated that, depending on the dose of propofol, the responsive sites for hypotensive effects may be different. Their studies were, however, done in atropinized animals.

Thus, the role of the autonomic nervous system in propofol-mediated hemodynamic changes remains controversial. Therefore, we conducted the present study to evaluate the dose-dependent effects of propofol on renal sympathetic nerve activity in urethane-anesthetized rabbits with an intact neuraxis, cervical vagotomy, sino-aortic denervation or the combined denervation of sino-aortic nerves and vagal nerves. Although its use is still controversial, we now used renal nerve activity as an index of overall sympathetic nerve responses, as we had done previously (Aibiki et al., 1988, 1994; Seki et al., 1997; Xu et al., 1998). Most of the earlier results were obtained during the continuous administration of propofol. Following a single low dose injection, propofol blood concentrations decrease rapidly as a result of quick redistribution and elimination (Reves et al., 1994). Thus, effects in the early phase after bolus injection should differ from those after bolus plus continuous infusion of propofol. In order to estimate the sympathetic responses to certain physiological stimuli, we need to check the early phase responses, because the responses develop within a few hundred milliseconds (Aibiki et al., 1994). Thus, we now chose the method of bolus injection of propofol. A preliminary experiment using conscious rabbits served to determine the doses of propofol given to animals.

2. Materials and methods

2.1. General procedures

This study was approved by the Institutional Animal Care Committee. Twenty-three white Japanese rabbits (body weight 2.2–3.5 kg) were anesthetized with intraperitoneal urethane (1.5 g/kg). After tracheostomy, respiration was maintained by positive pressure ventilation with room air after paralysis with gallamine triethiodide (4 mg/kg i.v.). Supplemental urethane (50–100 mg) and gallamine (5–10 mg) were given intravenously every 30 min, so that blood pressure, heart rate and sympathetic nerve activity would not change abruptly in response to some noxious stimuli. Mechanical ventilation was adjusted to control arterial blood gases within the physiological range. Heart rate was displayed by triggering the R wave of an electrocardiogram on lead II. Central venous pressure was measured simultaneously through a catheter placed in the superior vena cava. Polyethylene catheters were placed in the right femoral artery for measurement of systemic blood pressure and blood sampling, and in the femoral vein for administration of drugs, respectively. Mean systemic blood pressure was determined electronically. The left renal sympathetic nerves were exposed by a retroperitoneal approach, so that the animals were placed in the left side-up lateral position.

2.2. Recording and quantification of renal sympathetic nerve activity

The method for renal sympathetic nerve recording has been described in detail elsewhere (Aibiki et al., 1994; Seki et al., 1997; Xu et al., 1998). Briefly, the left renal sympathetic nerves were separated and placed on a bipolar silver electrode after immersion in liquid paraffin for recording sympathetic renal nerve discharges. The recorded discharges were amplified with a preamplifier (4124, Sanei, Nihon Denki, Japan). The amplified neurogram was rectified and integrated with a time constant of 2.0 s through an R–C integrator circuit. In order to standardize the values for sympathetic nerve activity obtained from animals that had a different number of active fibers, the resting nerve discharges before the injection were normalized to 100%. The noise level of renal sympathetic nerve activity obtained after the death of each animal was interpreted as the zero level of nerve activity. The renal sympathetic nerve activity levels after propofol administration were expressed as percentages of the resting nerve discharges before the injection.

2.3. Experimental protocol

After surgical preparation, 30 to 40 min were allowed for stabilization of all variables measured. Twenty three rabbits were divided into the following four groups: animals with an intact neuraxis (intact group: $n = 8$); animals with cervical vagal nerve sectioned but with intact carotid sinus and aortic nerves (vagotomy group: $n = 5$); animals with the carotid sinus and aortic nerve sectioned but with intact vagal nerves (SAD group: $n = 5$); and animals with the sino-aortic nerves and cervical vagal nerves denervated (SADV group: $n = 5$). In rabbits, we can selectively denervate aortic nerves from cervical vagal nerves. In the vagotomy, SAD, and SADV groups, acute hypertension associated with sympathetic activation occurred after denervation. However, after resting for approximately 30 to 40 min, hemodynamics and sympathetic nerve activity gradually returned toward the pre-denervation level. Completeness of sino-aortic denervation was confirmed by the absence of heart rate and renal nerve responses to a nitroglycerine-induced decrease and a phenylephrine-induced increase of 20–30 mm Hg in arterial blood pressure.

2.4. Preliminary experiment and propofol administration

In a preliminary experiment, we administered 2.5, 5, 10, and 20 mg/kg of propofol (1% Diprivan®, Zeneca Pharmaceuticals, Japan) to conscious rabbits with intact neuraxis ($n = 3$). A bolus dose of 10 mg/kg caused a marked

Table 1
Baseline values of heart rate, mean blood pressure and central venous pressure in each group
Values are means ± S.E. HR, heart rate; MBP, mean blood pressure; CVP, central venous pressure; SAD, sino-aortic denervation; SADV, SAD plus cervical vagotomy.

	HR (beats/min)	MBP (mm Hg)	CVP (mm Hg)
Intact group ($n = 8$)	308 ± 10	98 ± 5	3 ± 1
Vagotomy group ($n = 5$)	312 ± 9	104 ± 6	3 ± 1
SAD group ($n = 5$)	319 ± 8	108 ± 6[a]	4 ± 1
SADV group ($n = 5$)	316 ± 6	109 ± 7[a]	4 ± 1

[a] Express significant differences between the intact and the SAD or SADV groups ($P < 0.05$).

decrease of PaO_2 at 1 min after the injection, and some animals died after 20 mg/kg injection because of profound hypoxia and hypotension. Thus, we needed to adjust or control respiration, so we chose an experimental setting using anesthetized animals and at bolus loading doses of 2.5, 5, 10 as well as 20 mg/kg in all groups. In order to eliminate possible effects of the emulsion formulation of propofol on the parameters, 10% intralipos®, lipid emulsion harvested from beans, was administered to nerve-intact rabbits. However, heart rate, mean blood pressure and renal sympathetic nerve activity did not change at all even after 5 ml bolus injection of the agent.

2.5. Data processing and statistical analysis

Data were collected before and after propofol bolus injection for 5 min to compare changes in the parameters among the four groups. After denervation of cervical vagal nerves and/or carotid sinus nerves, sympathetic augmentation usually occurs. Thus, the baseline levels of sympathetic tone should differ among groups. It is hard to compare the data for nerve activity among groups. In this study, therefore, we did not compare the data for nerve activity among such groups. All values are reported as means ± S.E. In each group, the effects of each dose on the parameters were evaluated by means of a one-way analysis of variance (ANOVA) with repeated measures. The significance of differences between individual means was evaluated using ANOVA followed by Scheffe's F-test. The group differences in the baseline values were analyzed using the Mann–Whitney U-test. A P value of less than 0.05 was considered significant.

3. Results

As demonstrated in Table 1, the pre-injection level of heart rate, mean blood pressure and central venous pressure did not differ significantly among the groups except that mean blood pressure in the SAD and SADV groups were significantly higher than that in the intact group.

3.1. Intact group

As shown in Fig. 1A, heart rate did not change significantly even after 10 mg/kg administration, but after the dose of 20 mg/kg, it decreased from 310 ± 7 to 267 ± 7 bpm at 1 min and then returned to its baseline level. Augmented renal sympathetic nerve activity (135 ± 14%) occurred immediately after 5 mg/kg injection, but was not associated with significant changes in mean blood pressure. After 10 mg/kg injection, however, renal sympathetic nerve activity did not change while mean blood pressure decreased markedly at 1 min then recovered.

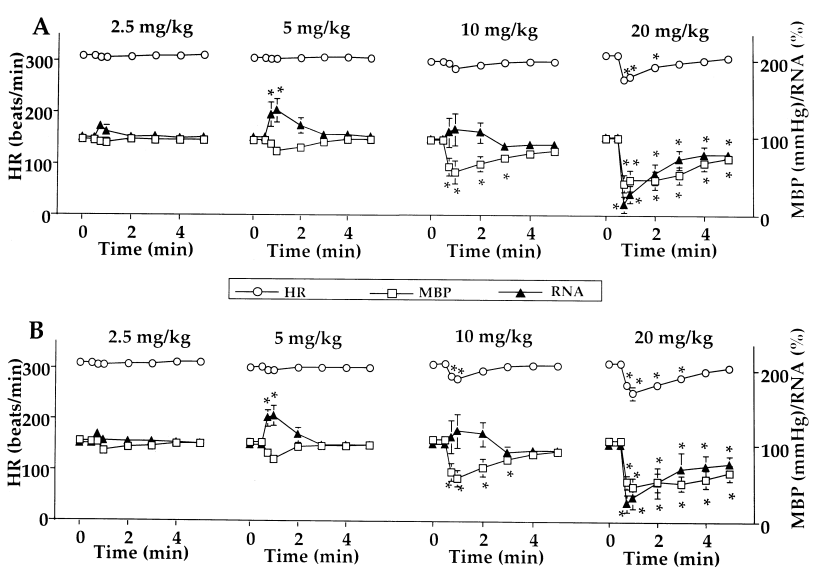

Fig. 1. Summarized data for heart rate (HR), mean blood pressure (MBP) and renal sympathetic nerve activity (RNA) in the intact group (A; $N = 8$), and vagotomy group (B; $N = 5$). Asterisks show significant differences as compared to each pre-injection value. Values are means ± S.E.

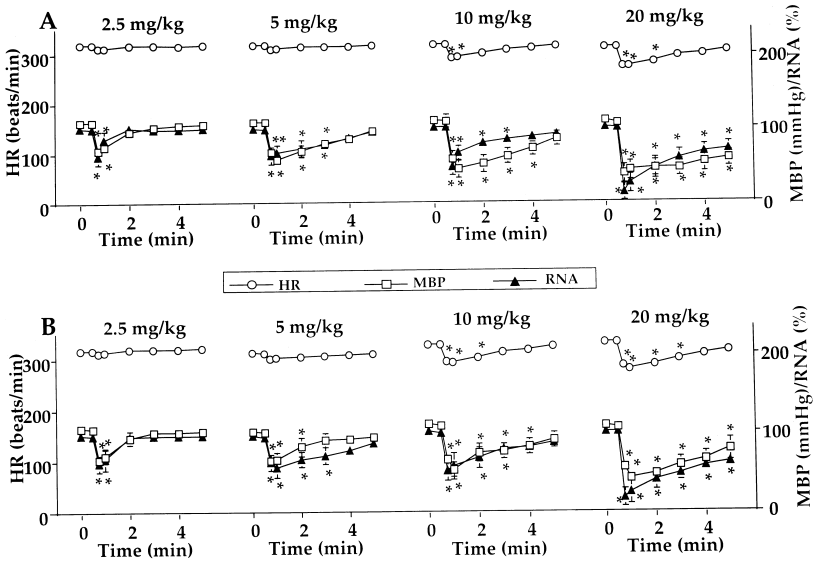

Fig. 2. Summarized data for heart rate (HR), mean blood pressure (MBP) and renal sympathetic nerve activity (RNA) in SAD group (A; $N = 5$) and SADV group (B; $N = 5$). Asterisks show significant differences as compared to each pre-injection value. Values are means ± S.E.

Renal sympathetic nerve activity declined to 16 ± 9% in parallel with a rapid decrease of mean blood pressure at 1 min after 20 mg/kg injection. These changes did not return to their pre-injection levels even after 5 min. Central venous pressure did not change significantly throughout the course. The changes in central venous pressure were also not significant in the three other groups.

3.2. Vagotomy group

As demonstrated in Fig. 1B, heart rate did not change significantly up to 5 mg/kg injection. After the injection of 10 and 20 mg/kg, heart rate declined then returned to their pre-injection levels. Renal sympathetic nerve activity increased to 139 ± 12% after 5 mg/kg injection, while mean blood pressure did not change greatly. After 10 mg/kg injection, there were no significant changes of renal sympathetic nerve activity, but mean blood pressure decreased. A sharp drop in renal sympathetic nerve activity associated with sustained hypotension occurred after loading of 20 mg/kg, and even after 5 min both were still significantly lower than before the injection.

3.3. SAD group

As illustrated in Fig. 2A, heart rate did not change significantly from its pre-injection level up to 5 mg/kg of propofol. However, after 10 and 20 mg/kg administration, heart rate declined significantly, but recovered after approximately 3 and 5 min. Renal sympathetic nerve activity diminished after each dose (2.5, 5, 10, and 20 mg/kg). Mean blood pressure dropped simultaneously. These changes were dose-dependent. The decreased responses of both renal sympathetic nerve activity and mean blood pressure did not return to their pre-injection levels even at 5 min after the injection.

3.4. SADV group

As presented in Fig. 2B, heart rate did not change significantly even after 5 mg/kg administration, but did fall after 10 and 20 mg/kg. Dose-dependent depressive responses of renal sympathetic nerve activity also occurred, associated with similar decreases of mean blood pressure. Renal sympathetic nerve activity was depressed; mean blood pressure decreased concurrently at 1 min. After the injection of 20 mg/kg, neither renal sympathetic nerve activity nor mean blood pressure returned to their pre-injection levels, even after 5 min.

4. Discussion

4.1. Role of the autonomic nervous system in propofol-induced hypotension

We have demonstrated in the present study that central sympathetic depression is a mechanism for propofol-induced hypotension in urethane-anesthetized rabbits, but that such effects were dependent on the dose of propofol given. At the lower dose of the agent in the intact and vagotomy groups, the hypotensive effects seem to be counteracted by the baroreflex system because augmented renal sympathetic nerve activity occurred after bolus injection up to 5 mg/kg, unaccompanied by significant changes in mean blood pressure and heart rate. Furthermore, loading of 10 mg/kg propofol decreased mean blood pressure significantly, but did not change renal sympathetic nerve

activity. At 20 mg/kg, deep depressions of renal sympathetic nerve activity together with sustained hypotension and bradycardia appeared. However, the sino-aortic-denervated groups showed dose-dependent depressions of renal sympathetic nerve activity in parallel with a decline of mean blood pressure. Thus, the current results indicated that propofol-induced depression of renal sympathetic nerve activity is centrally mediated, and that the baroreceptor reflex may not be inhibited by a lower dose of the agent. The present results also suggest that blood pressure control after propofol injection is exerted by the baroreceptor reflex system.

Different mechanisms for propofol-induced hypotension have been suggested: declines in myocardial contractility (Coetzee et al., 1989; Hettrick et al., 1997), in afterload (Claeys et al., 1988) or in preload (Goodchild and Serrao, 1989; Muzi et al., 1992). As now demonstrated, 10 mg/kg propofol caused significant drops in mean blood pressure but not in heart rate in the intact group. Furthermore, in the SADV group, where the baroreceptor reflex was abolished, propofol up to 5 mg/kg produced decreases in mean blood pressure but not in heart rate. These differential effects of the agent on mean blood pressure and heart rate suggest the possibility that the agent has (1) a strong vasodilating effect but a smaller negative choronotropic effect on the heart; or (2) a selective cardiac inhibitory inotropic effect. However, we must not neglect the possibility that, after propofol, there is a greater inhibition of sympathetic vascular output relative to cardiac sympathetic output regulating heart rate and cardiac contractility. These possibilities should be clarified in future studies measuring cardiac output and peripheral blood flow along with cardiac sympathetic nerve recordings.

In addition, propofol has been shown to reduce the tonic levels of muscle nerve sympathetic activity in humans (Sellgren et al., 1990, 1994; Ebert et al., 1992), and renal nerve activity in rats (Krassioukov et al., 1993, 1995), and to decrease plasma norepinephrine kinetics in dogs (Deegan et al., 1991) or to produce no changes in humans (Samain et al., 1989). Krassioukov et al. (1993, 1995) have reported that propofol-induced hypotensive effects after injection of a small dose of the agent are probably related to its direct action on the heart and/or the peripheral vasculatures because the central sympathetic control for the circulation was not markedly disrupted, while a high dose of propofol caused selective effects on the vasomotor neurons. However, based on the latter studies, the role of the autonomic nervous system and baroreceptors in propofol-induced hypotensive effects seems unclear. In the present study, we found that, in the intact group, to depress renal sympathetic nerve activity after a bolus injection requires a large dose of propofol, while a dose-dependent depression of renal sympathetic nerve activity with hypotensive effects developed in the sino-aortic denervated groups. The reduction of renal sympathetic nerve activity observed in the denervated animals even at the 2.5 mg/kg dose may reflect inhibition of the sympathetic outflow from the central nervous system. In the intact animals, augmented renal sympathetic nerve activity at lower doses of the agent, an effect which is likely to be mediated via baroreflexes, may be effective to overcome the blood pressure change induced by propofol. However, at higher doses of the agent, reductions of renal sympathetic nerve activity and mean blood pressure occurred simultaneously, which suggests that baroreceptor reflexes are impaired by the direct effects of the agent on the central nervous system. Thus, our results extend the previous findings that the propofol-induced hypotensive effects are the result of summed effects on baroreceptor reflex and central sympathetic depression caused by the agent, all of which depend on the dosage of propofol.

4.2. Effects of propofol on baroreflex and heart rate

We have now found that baroreflex function may not be inhibited by propofol at a low-dose injection. Augmented renal sympathetic nerve activity occurred even after 5 mg/kg bolus injection, unaccompanied by significant changes in either mean blood pressure or heart rate. Recently, there have been several conflicting reports regarding propofol effects on the baroreceptor reflex: no changes (Cullen et al., 1987; Samain et al., 1989), slight (Blake et al., 1988; Sellgren et al., 1992), and marked (Sellgren et al., 1990; Ebert et al., 1992; Kamijo et al., 1992) depressions of baroreflex sensitivity, which may vary depending on the experimental models or anesthesia. All of these results were, however, obtained during the continuous administration of propofol. According to our results, propofol-mediated sympathetic depression in nerve-intact animals requires a higher dose of the agent, a finding which is supported by other laboratory reports (Krassioukov et al., 1993, 1995). Following a single low-dose injection, propofol blood concentrations decrease rapidly as a result of quick redistribution and elimination (Reves et al., 1994). Thus, effects in the early phase after bolus injection should be different from those after bolus plus continuous infusion of propofol. In our intact and vagotomy groups, heart rate did not change significantly after a low dose of the agent in spite of augmented renal sympathetic nerve activity. Even in the SAD and SADV groups, heart rate did not decrease at the doses of 2.5 and 5 mg/kg of the agent whereas renal sympathetic nerve activity was greatly depressed. Although discussions of these results may be limited because of the limited variables measured in this study, the possible but interesting explanations, relating to the regional differences in sympathetic output (Koyama et al., 1992; Matsukawa et al., 1993), are as follows: (1) central sympathetic outflow regulating heart rate may be inhibited to a lesser extent by propofol relative to other sympathetic outflows; or (2) the renal sympathetic nerve activity increase represents a general sympathetic activity increase, including cardiac sympathetic activity

regulating heart rate, and a depression of central sympathetic outflow by propofol can be compensated by a baroreflex input eliciting enhanced sympathetic outflow, thereby preserving heart rate and mean blood pressure in intact and vagotomized animals. However, to settle this point, we need to perform further studies with simultaneous measuring of renal and cardiac sympathetic nerve activity.

Effects of propofol on heart rate are still contentious, with reports ranging from no change (Coates et al., 1987; Claeys et al., 1988) to increases (Muzi et al., 1992; Wouters et al., 1995) and even decreases (Cullen et al., 1987; Brüssel et al., 1989) after injection. Propofol-induced bradycardia is thought to be due to (1) a direct effect on sinus nodes (Colson et al., 1988), and (2) possible mediation of vagal nerves (Cullen et al., 1987; Deutschman et al., 1994). In the present study, heart rate did not change significantly with a low dose of propofol, while bradycardia developed with a higher dose in all groups. The occurrence of bradycardia at higher doses may be attributable to the predominance of the direct effects on the heart. Furthermore, the changes of heart rate in vagotomized animals were similar to those in the nerve-intact animals, and therefore we could find no basis for vagotonic bradycardia after propofol injection. A recent paper, using the evaluation of heart rate variability, has shown a possible role of the parasympathetic-nervous system in propofol-induced bradycardia (Deutschman et al., 1994). However, the authors used fentanyl, a potent parasympathotonic agent (Honda et al., 1994), with propofol. Therefore, it is difficult to define the effects of propofol alone on the autonomic nervous system. In the present study, we have clearly demonstrated different responses of heart rate and of sympathetic nerve activity: despite augmented renal sympathetic nerve activity, no significant changes in heart rate were found. Thus, these data may show that there are limits to the use of heart rate variability to evaluate autonomic nerve responses.

4.3. Limitations of the study

There are several limitations to this study. According to our preliminary experiment using conscious rabbits, it was necessary to perform this study in anesthetized animals because of profound hypoxia and hypotension, which may therefore have produced different results from the clinical setting. With the experimental settings we now used, we have demonstrated for the first time a dose-dependent effect of propofol on sympathetic nerve activity and hemodynamics. However, further studies using conscious animals are required to define the role of the autonomic nervous system in propofol-induced hemodynamic changes. Some concerns regarding the use of renal nerve activity as an index for the overall sympathetic responses may emerge. Regional differences between cardiac and renal sympathetic nerve activity have been reported (Matsukawa et al., 1993), but Koyama et al. (1992) have demonstrated, using multi-site recordings of sympathetic nerve activity, that similar responses at different measuring sites were found with rapidly applied physiological stimuli such as hemorrhagic hypotension at least. Thus, regional differences in sympathetic responses are still controversial.

In summary, propofol-mediated hypotension is due in part to inhibition of the central sympathetic nervous system. Baroreceptor reflexes seem not to be impaired by a low dose of propofol. In fact, the baroreceptor reflex may be preserved at the lower dose of the agent. Propofol does not cause significant changes of heart rate on low-dosage injection, but bradycardia can be induced by a large dose. Differential effects on heart rate and mean blood pressure may indicate a greater inhibition of sympathetic vascular outflow relative to cardiac sympathetic outflow regulating cardiac rate and contractility.

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