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# Anesthetic induction agents, sympathetic nerve activity and baroreflex sensitivity: a study in rabbits comparing thiopental, propofol and etomidate.

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## Abstract

The mechanisms of arterial hypotension following intravenous anesthetic induction agents are multifactorial. The purpose of this study was to evaluate and compare the effects of thiopental, propofol and etomidate on hemodynamics, sympathetic outflow and arterial baroreflex sensitivity using not only neuraxis-intact but also totally baro-denervated rabbits. A total of 60 rabbits was anesthetized with urethane, tracheotomized, and mechanically ventilated with oxygen in nitrogen (FiO2 0.5). The left renal sympathetic nerve was isolated and placed on a bipolar electrode to record renal sympathetic nerve activity (RSNA). Thirty animals underwent a surgical preparation of total baroreceptor denervation. Bolus injections of an anesthesia induction dose of thiopental 4 mg/kg and twice the induction dose of propofol 4 mg/kg significantly decreased RSNA to the same extent (19.4+/-6.7 and 19.7+/-5.2% reduction, mean +/- SEM) and mean arterial pressure (MAP) also to the same extent (19.5+/-4.6 and 22.1+/-3.1% reduction) in the neuraxis-intact animals. RSNA was increased (34.5+/-6%) without reduction of MAP by an induction dose of etomidate, 0.3 mg/kg. Sympathetic barosensitivity was attenuated even 10 min after thiopental at 4 mg/kg or propofol at 4 mg/kg (68% and 54% of control, respectively). Propofol at 2 mg/kg (induction dose) and etomidate at 0.6 mg/kg decreased RSNA and MAP only in the baro-denervated animals. It was found from the barosensitivity study that patients can be hemodynamically unstable even though blood pressure has returned to normal after thiopental and propofol administration. Data suggest that etomidate can even stimulate the sympathetic nervous system and increase sympathetic outflow. It was also clearly found from the baro-denervated animal study that thiopental was stronger than propofol in directly suppressing sympathetic outflow at the induction dose.

**KEYWORDS:** intravenous anesthetics, sympathetic outflow, baroreflex

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*Original Article*

# Anesthetic Induction Agents, Sympathetic Nerve Activity and Baroreflex Sensitivity: A Study in Rabbits Comparing Thiopental, Propofol and Etomidate

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**The mechanisms of arterial hypotension following intravenous anesthetic induction agents are multifactorial. The purpose of this study was to evaluate and compare the effects of thiopental, propofol and etomidate on hemodynamics, sympathetic outflow and arterial baroreflex sensitivity using not only neuraxis-intact but also totally baro-denervated rabbits. A total of 60 rabbits was anesthetized with urethane, tracheotomized, and mechanically ventilated with oxygen in nitrogen ($FiO_2$ 0.5). The left renal sympathetic nerve was isolated and placed on a bipolar electrode to record renal sympathetic nerve activity (RSNA). Thirty animals underwent a surgical preparation of total baroreceptor denervation. Bolus injections of an anesthesia induction dose of thiopental 4 mg/kg and twice the induction dose of propofol 4 mg/kg significantly decreased RSNA to the same extent ($19.4 \pm 6.7$ and $19.7 \pm 5.2\%$ reduction, mean $\pm$ SEM) and mean arterial pressure (MAP) also to the same extent ($19.5 \pm 4.6$ and $22.1 \pm 3.1\%$ reduction) in the neuraxis-intact animals. RSNA was increased ($34.5 \pm 6\%$) without reduction of MAP by an induction dose of etomidate, 0.3 mg/kg. Sympathetic barosensitivity was attenuated even 10 min after thiopental at 4 mg/kg or propofol at 4 mg/kg (68% and 54% of control, respectively). Propofol at 2 mg/kg (induction dose) and etomidate at 0.6 mg/kg decreased RSNA and MAP only in the baro-denervated animals. It was found from the barosensitivity study that patients can be hemodynamically unstable even though blood pressure has returned to normal after thiopental and propofol administration. Data suggest that etomidate can even stimulate the sympathetic nervous system and increase sympathetic outflow. It was also clearly found from the baro-denervated animal study that thiopental was stronger than propofol in directly suppressing sympathetic outflow at the induction dose.**

**Key words:** intravenous anesthetics, sympathetic outflow, baroreflex

Arterial hypotension occurs through various mechanisms after the intravenous (i.v.) administration of anesthetic induction agents such as thiopental and propofol. These mechanisms include negative inotropic action [1-3], vasodilation with reduced preload and afterload [4-7], and depression of the sympathetic nervous system with reduced sympathetic outflow and attenuated baroreflex integrity [8-10]. Thiopental has been a popular i.v. anesthetic induction agent for many decades. However, propofol, a diisopropylphenol i.v.

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hypnotic agent, is gaining popularity because of patients' rapid recovery from anesthesia and its antiemetic properties, although its hypotensive action may be stronger than thiopental. Etomidate, another i.v. induction agent, is known to have minimal effects on the sympathetic nervous system. The main purpose of the present study was to determine which is stronger in depressing sympathetic outflow, thiopental or propofol, and to reveal the direct and unmasked effect of etomidate on sympathetic outflow, using totally baro-denervated animals in addition to neuraxis-intact animals.

## Materials and Methods

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

***General preparation.*** New Zealand white rabbits, weighing 2.8 to 3.4 kg were anesthetized by means of intravenous (i.v.) administration of urethane at 1 g/kg. Anesthesia was maintained with supplemental administration of i.v. urethane at 100 mg/kg/h throughout the experiment. The animals were tracheotomized, intubated, and mechanically ventilated with an infant ventilator (Model LS 104 150; Bourns Life System, Riverside, CA, USA) using 50% oxygen in nitrogen at a tidal volume of 10–15 ml/kg and a frequency of 25–30 cycles/min. Acid-base balance was maintained within normal limits ($PaCO_2$ 35–45 mmHg; pH 7.35–7.45) by adjusting the tidal volume and ventilatory frequency. Polyethylene catheters were placed in a femoral vein for i.v. administration of drugs and in a femoral artery for measurement of arterial pressure and sampling of arterial blood. The animals were paralyzed intermittently with i.v. vecuronium 0.1 mg/kg to facilitate ventilation and to avoid artifacts on the measurement of sympathetic nerve activity secondary to muscular movement. Arterial blood pressure was monitored using a pressure transducer (DTX Spectramed, Oxnard, CA, USA) and was recorded continuously. Mean arterial pressure (MAP) was derived by electronic integration of the pulsatile pressure signal. Heart rate (HR) was calculated from lead II of the electrocardiogram using a cardiotachometer (Model 1321; San-ei, Tokyo, Japan). Both MAP and HR were recorded throughout the experiment along with renal sympathetic nerve activity (RSNA) on a multichannel recorder (Omnicorder 8M14; San-ei, Tokyo, Japan). Body temperature was maintained between 36.5 °C and 37.5 °C by means of an external warming apparatus.

***Recording of renal sympathetic nerve activity*** [11, 12]. The left kidney was exposed retroperitoneally by a left flank incision. The renal sympathetic nerve along with the renal artery was isolated using a microscope. The distal ends of the strands were crushed, and the sympathetic nerve was immersed in mineral oil and placed on a bipolar silver electrode for recording the nerve discharges. The raw nerve signals were amplified by a preamplifier (AVB 10: bandwidth = 50–3000 Hz, Nihon Kohden, Tokyo, Japan). The amplified nerve signals were visualized on a dual-beam oscilloscope (VCX 11, Nihon Koden, Tokyo, Japan) and monitored by means of an audio speaker. Integrated renal sympathetic nerve activity (RSNA) was obtained by integrating the rectified signal with a time constant of 2.0s, using a resistance-capacitance integrator circuit. Nerve activity was recorded after death in all rabbits as a measurement of the level of zero "noise."

***Total baroreceptor denervation.*** The bilateral cervical vagi were exposed and severed. Sinoaortic denervation was performed by using a dissecting microscope. We isolated the bilateral bifurcation of the external and internal carotid artery from sympathetic and vagus ganglions, then we cut bilateral aortic depressor nerves, removed all nerve fibers attached to the carotid artery, and stripped the adjacent connective tissues. Total baroreceptor denervation was confirmed by the absence of an increase or decrease in HR and RSNA in response to i.v. sodium nitroprusside (15 $\mu$g/kg) or phenylephrine (5 $\mu$g/kg).

***Experimental protocol.***

1. Intact Group

After surgical preparation and hemodynamic stabilization, 30 neuraxis-intact rabbits were divided into 5 groups of 6 each: propofol at 2 mg/kg (P2 Group), propofol at 4 mg/kg (P4 Group), etomidate at 0.3 mg/kg (E 0.3 Group), etomidate at 0.6 mg/kg (E 0.6 Group) or thiopental at 4 mg/kg (T4 Group). Each bolus injection of the drug was carried out in 5 sec through the femoral vein. All variables were monitored and recorded for 30 min after injection. An arterial baroreflex depressor test was carried out by i.v. administration of nitroprusside (10 $\mu$g/kg) before, and 10 and 30 min after each bolus injection of the study agents. Arterial barosensitivity was assessed by calculating the ratio of increments of % RSNA to nitroprusside-induced reduction of MAP ($\Delta$%

RSNA/ΔMAP) before, and 10 and 30 min after injection (11).

2. Baro-denervated Group

Thirty rabbits were divided into 5 groups of 6 each: propofol at 2 mg/kg (D-P2 Group), propofol at 4 mg/kg (D-P4 Group), etomidate at 0.3 mg/kg (D-E 0.3 Group), etomidate at 0.6 mg/kg (D-E 0.6 Group), or thiopental at 4 mg/kg (D-T4 Group). Each bolus injection of the drug was carried out as in the intact groups, and all variables were monitored and recorded for 15 min after injection.

***Statistical analysis.*** All data were expressed as mean ± SEM. Statistical analysis was performed using repeat-measure analysis of variance, followed by means comparisons of contrasts for within-group comparison and by Fisher's new multiple range method for between-group comparison (Super ANOVA, Abacus Concepts, Inc., Berkeley, CA, USA). Differences with a statistical probability of less than 0.05 were considered significant.

## Results

The accompanying table shows baseline values of HR and MAP in neuraxis-intact and baro-denervated animals. No significant differences in HR and MAP existed between agents and doses in each group.

Time course % change of MAP, RSNA, and HR in the neuraxis-intact group are shown in Fig. 1–3. (Error

**Table 1** Baseline Values of HR and MAP

| Neuraxis-Intact Group (mg/kg) | P2 | P4 | T4 | E0.3 | E0.6 |
|---|---|---|---|---|---|
| HR (beats/min) | 280.2 ± 7.7 | 285.3 ± 3.8 | 289.0 ± 7.1 | 291.0 ± 4.0 | 277.6 ± 9.9 |
| MAP (mmHg) | 87.2 ± 4.7 | 91.8 ± 3.2 | 95.3 ± 3.5 | 88.2 ± 3.2 | 93.6 ± 4.5 |
| **Baroreceptor-denervated Group (mg/kg)** | **D-P2** | **D-P4** | **D-T4** | **D-E0.3** | **D-E0.6** |
| HR (beats/min) | 343.8 ± 7.8 | 334.5 ± 6.3 | 328.5 ± 5.3 | 338.8 ± 9.3 | 336.4 ± 8.8 |
| MAP (mmHg) | 107.8 ± 6.6 | 106.4 ± 5.9 | 106.8 ± 4.6 | 105.8 ± 6.3 | 108.3 ± 6.7 |

Values are mean ± SEM. D-, totally baro-denervated. E, etomidate; P, propofol; T, thiopental.

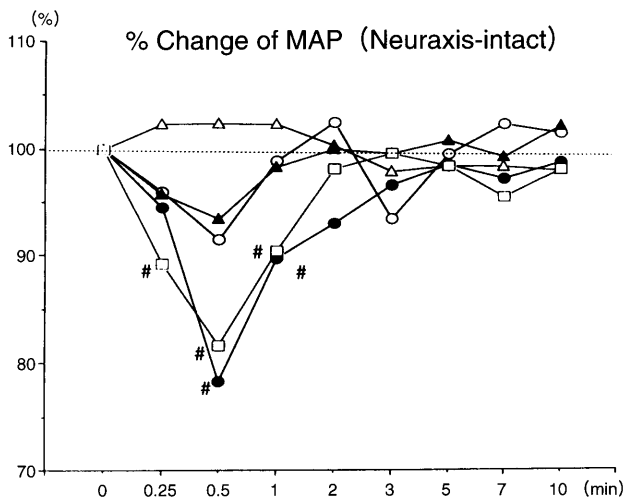


**Fig. 1** Change of mean arterial pressure (MAP). —●—, propofol 2 mg/kg (P2); ●, propofol 4 mg/kg (P4); —△—, etomidate 0.3 mg/kg (E0.3); —▲—, etomidate 0.6 mg/kg (E0.6); —□—, thiopental 4 mg/kg (T4); #, $P < 0.05$ *vs.* before injection. Error bars are omitted for clarity.
Note: Significant reduction of MAP after P4 and T4.

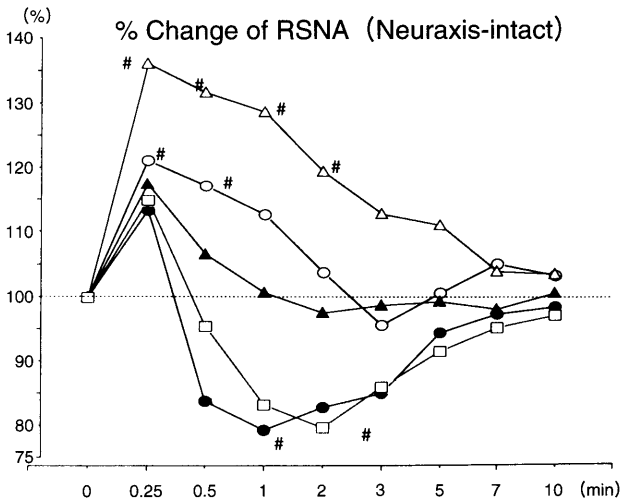


**Fig. 2** Change of renal sympathetic nerve activity (RSNA).
Note: Significant increases in RSNA after P2 and E0.3 and decreases after P4 and T4.
See footnotes of Fig. 1 for symbols.

bars are omitted for clarity. Symbols for statistically significant differences in the between-group comparison are also omitted and only significant differences necessary for discussion are stated in the text and in the footnotes of figures.) In the P4 and T4 groups, MAP and RSNA decreased and HR increased significantly. The percent maximum reduction of MAP was $-22.1 \pm 3.1\%$ in the P4 Group, and $-19.5 \pm 4.6\%$ in the T4 group. Maximum reduction of RSNA was very similar in both groups; $-19.7\% \pm 5.2\%$ and $-19.4 \pm 6.7\%$, respectively. MAP, RSNA and HR did not change significantly in the E 0.6 group.

In the E 0.3 group, RSNA increased significantly (maximum increase $+34.5 \pm 6.7\%$), without reduction of MAP.

Fig. 4 shows that the arterial baroreceptor sensitivity was significantly attenuated even 10 min after propofol at 4 mg/kg and thiopental at 4 mg/kg injections. Fig. 5-7 show time course % change of MAP, RSNA, and HR in totally baro-denervated animals. There were prolonged and marked reductions of MAP, RSNA, and HR in the D-P4 and D-T4 groups ($P < 0.05$). MAP and RSNA decreased significantly in the D-P2 and D-E 0.6 groups, but the degree of reduction was significantly less ($P < 0.05$) than in the D-P4 and D-T4 groups. None of the variables changed significantly in the D-E 0.3 group.

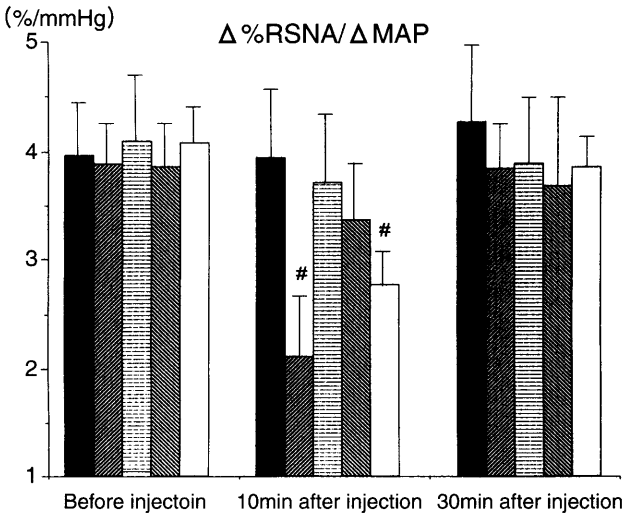


**Fig. 4** Arterial barosensitivity as determined by depressor test. Δ % RSNA/ΔMAP; ratio of % increase of renal sympathetic nerve activity to nitroprusside-induced reduction of mean arterial pressure. ■, propofol 2 mg/kg; ▨, propofol 4 mg/kg; ▤, etomidate 0.3 mg/kg; ▧, etomidate 0.6 mg/kg; □, thiopental 4 mg/kg; #, $P < 0.05$ *vs.* before injection

Note: Arterial barosensitivity was significantly impaired even after 10 min of P4 and T4 injection.

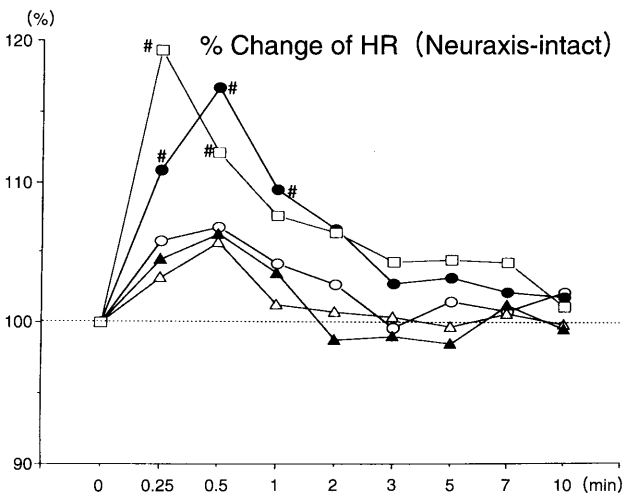


**Fig. 3** Change of heart rate (HR).

Note: Significant increase in HR after P4 and T4.

See footnotes of Fig. I for symbols.

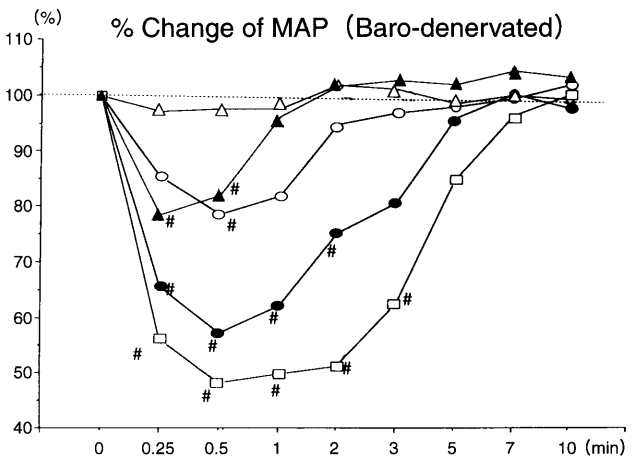


**Fig. 5** Change of mean arterial pressure (MAP).

# $P < 0.05$ *vs.* before injection.

Note: Reduction of MAP is greater with thiopental at 4 mg/kg than with propofol 4 mg/kg ($P < 0.05$).

See footnotes of Fig. I for symbols.

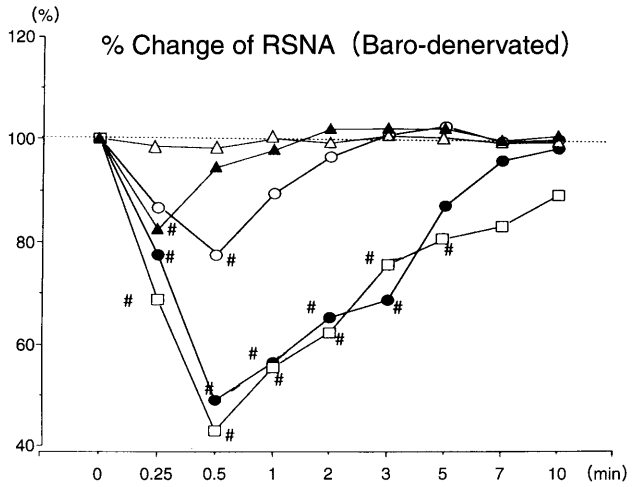


**Fig. 6** Change of renal sympathetic nerve acitvity (RSNA).
Note: The degree of significantly and similarly decreased RSNA with thiopental at 4 mg/kg and propofol at 4 mg/kg was greater than that with propofol at 2 mg/kg and etomidate at 0.6 mg/kg ($P < 0.05$).
See footnotes of Fig. I for symbols.

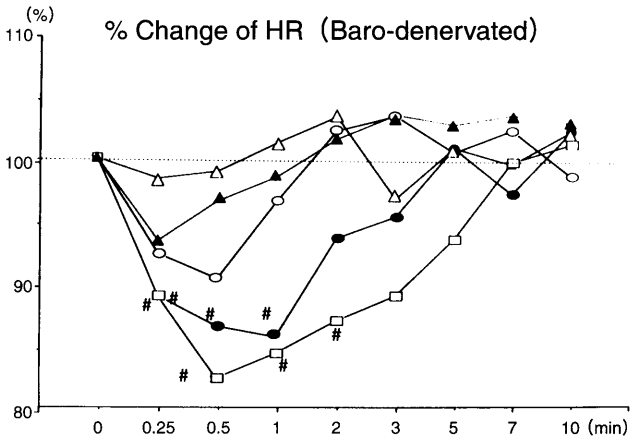


**Fig. 7** Change of heart rate (HR).
Note: There are significant reductions of HR after P4 and T4.
See footnotes of Fig. I for symbols.

## Discussion

It is generally accepted that i.v. bolus doses of propofol at 2 mg/kg, thiopental at 4 mg/kg and etomidate at 0.3 mg/kg are approximate induction doses of anesthesia in humans [7, 13, 14]. We used induction doses of these agents and twice the induction doses of propofol and etomidate for a dose-response study. Thiopental, 8 mg/kg, which is twice the induction dose for humans, was not used since it produced severe hypotension and occasionally cardiac arrest in the preliminary study. Because of complicated surgical preparations, chronically instrumented animals could not be utilized in our study.

Urethane was used for basal anesthesia since it does not affect arterial baroreflex sensitivity and produces long-lasting anesthesia with minimal cardiovascular depression [15, 16]. Urethane might have potentiated these i.v. agents; however, we assumed that the basal anesthesia with urethane produced comparable physiological conditions for each agent. Because of easy accessibility, renal sympathetic nerve activity was measured and it represents overall sympathetic outflow from the central nervous system. [11, 12]

It has been shown that propofol and thiopental decrease sympathetic nerve activity in humans [9, 17, 18]. In the neuraxis-intact animals, it was found that propofol 4 mg/kg and thiopental 4 mg/kg were equipotent in decreasing MAP and also RSNA (Figs. 1, 2). HR was increased in both groups (Fig. 3), even though decreased sympathetic outflow as indicated by decreased RSNA should have acted to decrease HR. As well recognized in humans [19], the increased HR was partly due to increased sympathetic activity but mainly due to overwhelmed baroreflex-mediated reduction of vagal activity in response to arterial hypotension. This is true, since HR was significantly decreased following administration of these agents in the baro-denervated animals where the vagus was eliminated (Fig. 7). RSNA was significantly increased at 0.25 and 0.5 min after propofol, 2 mg/kg administration in the neuraxis intact group. This is likely because baroreflex-mediated increase in sympathetic nerve activity in response to arterial hypotension overwhelmed the direct inhibitory action of propofol at 2 mg/kg on the sympathetic nervous system.

A sympathetic barosensitivity study can be performed only in the neuraxis-intact group for an obvious reason. RSNA increases or decreases in response to a decrease or increase in MAP through the intact baroreflex pathway. We performed baroreflex depressor tests, using sodium nitroprusside, and $\Delta$%RSNA/$\Delta$MAP indicates an increment of %RSNA by 1 mm Hg reduction of MAP. The smaller number as compared to control values indicates a greater degree of attenuation of baroreflex sensitivity. It has been demonstrated that sympathetic baroreflex sensitivity was impaired during thiopental infusion [18] and during steady state propofol anesthesia [9]. Even after

MAP and RSNA returned to the baseline values, sympathetic barosensitivity was still impaired in the P4 and T4 groups (Fig. 4). This may explain why patients are prone to develop arterial hypotension in response to opioids, inhalation anesthetics, *etc.*, although blood pressure is back to normal several minutes after single administration of these i.v. induction agents. Nevertheless, decreased sympathetic outflow and impaired arterial barosensitivity contributed to a significant reduction of MAP in the P4 and T4 groups, in addition to direct negative inotropic and vasodilatory actions.

Etomidate has been found not to decrease sympathetic outflow [1], nor to attenuate baroreflex sensitivity [8, 10]. As stated in the human study by Ebert *et al.* [10], our animal data also indicate that clinically stable hemodynamics after etomidate are due to a minimal suppression of the sympathetic outflow and unimpaired baroreflex sensitivity. Moreover, RSNA increased significantly with E 0.3 in the neuraxis-intact animals without reduced MAP (Fig. 2), suggesting that a low dose of etomidate can even stimulate the sympathetic nervous system. On the other hand, E 0.3 did not increase RSNA in the baro-denervated group. Since both arterial and cardiopulmonary baroreflexes were eliminated in the totally baro-denervated animals, changes in RSNA reflected direct and unmasked effects of the studied i.v. induction agents on the sympathetic nervous system. However, baseline activity of the sympathetic nerve activity was inevitably increased by total baro-denervation. Therefore, it can be speculated that already increased sympathetic nerve activity was not increased appreciably further by the slight stimulatory action of 0.3 mg/kg of etomidate in the baro-denervated animals. Nevertheless, data from the baro-denervated animals (Figs. 5, 6) may indicate that etomidate does not necessarily guarantee stable hemodynamics in baroreflex-impaired patients such as diabetic and elderly patients.

It is of interest to note that in the baro-denervated animals, the degree of hypotension in the D-T4 group was greater than that in the D-P4 group ($P < 0.05$), although the degrees of reduction of RSNA were very similar (Figs. 5, 6). This may suggest that direct negative inoptropic action and direct vasodilation might have contributed to the reduced MAP more with thiopental than with propofol at the same mg weight basis. In the past, there have been ambiguous findings as to which exerts more direct cardiovascular depression, thiopental or propofol. Gelissen *et al.* demonstrated that thiopental but not propofol showed strong negative inotropic properties on isolated human atrial muscle [3]. Park and his colleague found that propofol depresses myocardial contractility less than thiopental at clinical plasma concentration ranges in isolated guinea pig ventricular muscle [20]. Other investigators found that propofol is a more potent vasodilator than thiopental in humans [4].

Because of bilateral vagotomy with interrupted cardiopulmonary baroreflex, decreased MAP in the D-P4 and D-T4 groups could not elicit reflex increase in HR, and HR was decreased probably due to markedly decreased sympathetic outflow (Fig. 7).

In summary, our data show that the order of direct suppressive effect on sympathetic outflow was: thiopental (induction dose, 4 mg/kg) $\cong$ propofol (4 mg/kg) $>$ propofol (induction dose, 2 mg/kg) $\cong$ etomidate (0.6 mg/kg). These data suggest that etomidate (at an induction dose) can even increase sympathetic outflow, contributing to stable induction of anesthesia. However, data from the baro-denervated animals suggest that etomidate does not guarantee stable hemodynamics in baroreflex-impaired patients. The data also suggest that barosensitivity may be attenuated for many minutes after thiopental and propofol administration, which may lead to an unstable hemodynamic condition.

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