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Effects of Propofol Intravenous Injection Bolus on the Left Ventricular Function and the Myocardial β-Adrenoceptor in Rats

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Abstract

Propofol bolus injection has been reported to influence cardiovascular functions. However, the detailed mechanism underlying this action has not been elucidated. This study was designed to investigate the effects of propofol *i.v.* bolus on the left ventricular function, the myocardial β-adrenoceptor (β-AR) binding-site density (Bmax) and Kd (apparent dissociation constant) in a 30-minute period. One hundred and four male Wistar rats were randomly divided into four groups: group C (control group), group I (intralipid group), group P1 (5mg/kg propofol) and group P2 (10 mg/kg propofol). The results showed a significant downregulation of HR, LVSP, $+dp/dt_{max}$ and $-dp/dt_{max}$ in both groups P1 and P2 (especially after bolus injection in 7 min) than those of group C ($P < 0.05$), whereas no significant difference was found between the P1 and P2 groups ($P > 0.05$). Likely, Bmax was remarkably upregulated in both groups P1 and P2 ($P < 0.05$, *vs.* groups C and I), and there was no significant difference between these two groups ($P > 0.05$). Of note, the Kd value in group P2 (10 mg/kg propofol) was found dramatically increased in 30 min than that in the low-dose propofol-treated group (group P1) as well as in groups C and I ($P < 0.05$). In conclusion, these results indicate that intravenous injection of propofol bolus can inhibit the cardiac function partially *via* upregulation of Bmax and downregulation of the β-AR affinity at higher-dose injection of propofol bolus.

Key Words: propofol, model, rat, myocardial β-adrenoceptor

Introduction

Propofol is widely used as a sedative in the theatre because it can be easily titrated and offers rapid recovery. While used for sedation or induction of anesthesia, propofol has been shown to have a number of hemodynamic effects, including substantial reductions in heart rate, cardiac output, arterial blood pressure, systemic vascular resistance (4, 10), and myocardial β-adrenoceptor responsiveness *in vitro* (18).

β-adrenoceptors (β-ARs) play important roles [U10] in the mediation of adrenergic control of cardiac muscle contraction, and any alterations in the dynamics of these receptors would affect myocardial function as a pump (14). Propofol bolus injection has been reported to influence cardiovascular functions. Although previous data have shown that injection of propofol may depress cardiac function in part *via* antagonism of β-adrenoceptor binding and, thus, receptor activation *via* catecholamines (18), the *in vivo* changes of myocardial β-ARs and cardiac function during 30 min after propofol *i.v.* has not been well described. The present study was undertaken to investigate the *in vivo* effects of propofol on the cardiac function, myocardial β-adrenoceptor density (Bmax) and affinity (Kd value) in a 30-min period after propofol *i.v.* bolus.

Materials and Methods

This study was approved by the Institutional

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Animal Care and Use Committee in accordance with the ethical principles provided by the Experimental Animal Laboratory of the School of Medicine, Sun Yat-Sen University. Male Wistar rats, weighing 250-300 g, were maintained in wire mesh cages with standard laboratory feed and water ad libitum under a 12 h light-dark cycle at 22°C. Propofol was purchased from Palazzo Volta-Via F.Sforza-20080 Basiglio (Milano), AstraZeneca, Italy.

Experimental Protocol

Experiments were designed as follows: left ventricular function assay (n = 32); detection of myocardial β-adrenoceptor density and affinity (n = 72). A total number of 104 animals were used in this study.

Left Ventricular Function Assay

A total number of 32 male Wistar rats were anesthetized with sodium pentobarbital (45 mg/kg intraperitoneally), with supplementary doses as required. After tracheotomy and tracheal intubation, a 22-gauge catheter was inserted into the right femoral vein for fluid infusion. Haemodynamic variables were measured by inserting a 2 Fr high-fidelity micromanometer catheter into the right carotid artery and then advancing it into the left ventricle, where it was secured. The position was confirmed by a characteristic decrease in diastolic pressure that occurred when the catheter was passing across the aortic valve into the left ventricular cavity. The high-fidelity micromanometer catheters were connected to the pressure transducers (BL-420E, TaiMeng, PRC). Wistar rats were randomly divided into four groups: control group (group C), intralipid group (group I), low-dose propofol (group P1) and high-dose propofol (group P2). Each group was divided into three subgroups (n = 6). Groups P1 and P2 accepted 5 mg/kg and 10 mg/kg propofol bolus intravenous injection, respectively, while groups C and I were given saline or intralipid intravenous injection, respectively. The total amount of propofol injection was calculated according to the animal's weight (kg), and the infusion speed was 0.1 ml per 5 seconds. Heart rate (HR), left ventricle pressure (LVSP), left ventricular end-diastolic pressure (LVEDP) and the maximum/minimum rate of LVSP ($+dp/dt_{max}$, $-dp/dt_{max}$) were measured at different times: baseline (before treatment), 1 min, 2 min, 3 min, 5 min, 7 min, 10 min, 15 min, 20 min, 25 min and 30 min after propofol was injected.

Myocardial β-Adrenoceptor Density and Affinity Measurement

A total number of 72 male Wistar rats were randomly divided into four groups: group C (control group), group I (intralipid group), group P1 (5 mg/kg propofol) and group P2 (10 mg/kg propofol). Each group was divided into three subgroups (n = 6). After successful establishment of the experimental model, the rats were sacrificed and dissected after injection for 3, 10 and 30 min, and their hearts were rapidly removed and perfused with ice-cold saline. The ventricles were then frozen and stored at –80°C for further experiments.

Membrane Preparation

Thawed ventricles were weighed, finely minced with scissors, and then immersed in 5 ml of ice-cold buffer containing 250 mM of sucrose, 5 mM of Tris hydrogen chloride and 1 mM of magnesium chloride, pH 7.4. Homogenization was obtained after three consecutive 20-sec bursts with a homogenizer (Polytron™, Heidolph, Kelheim, Germany), and the homogenate was diluted with an additional ten volumes of buffer, strained through four layers of gauze, and centrifuged at 500 g for 10 min at 4°C. The resulting supernatant fluid was carefully decanted from the pellet and then centrifuged at 48,000 g for 20 min. The pellet was resuspended in 5 ml of 50 mM of Tris-hydrogen chloride, 10 mM of magnesium chloride, pH 7.4, and washed twice by centrifugation at 48,000 g for 20 min. The final pellet was resuspended in 5 ml of 50 mM of Trishydrogen chloride and 10 mM of magnesium chloride, pH 8.0. The protein content was determined according to the method of Lowry *et al*. (9), and the solution was adjusted to produce a final concentration of 5 mg protein/ml.

Radioligand Binding Assay

The beta-receptor binding assay was performed as described by Feldman *et al*. (1983). L-sup 125 I-iodocyanopindolol (2,200 Ci/mM, Amersham Corporation, Arlington Heights, IL) was used as a radioligand. Cardiac membranes were incubated with 125 iodocyanopindolol for 120 min at 37°C in a final volume of 250 ml, containing 0.6 mM of ascorbic acid, 60 mg/ml of bovine serum albumin, 0.03 mM of phentolamine mesylate, 12 mM of Trishydrogen chloride (pH of 7.4 at 37°C), 0.054% sodium chloride, 7.5 mM of magnesium chloride, and 0.9 mM of EDTA. Duplicate measurements of bound 125 iodocyanopindolol were performed for eight different concentrations ranging from 6 to 360 pM in each assay. The reaction was terminated by the addition of 15 ml of 0.9% sodium chloride, 10 mM of Tris-hydrogen chloride and 12.5 mM of magnesium chloride, followed by

Table 1. Effects of propofol on the HR in 30 min (n = 8, means ± SD)

Time	**HR** (beat/min)			
	Group C	Group I	Group P1	Group P2
Baseline	414 ± 31	414 ± 30	414 ± 24	427 ± 22
1 min	415 ± 29	415 ± 26	352 ± 43**$^{\Delta}$	328 ± 23**$^{\Delta\Delta}$
2 min	415 ± 29	415 ± 29	373 ± 31*$^{\Delta}$	326 ± 52**$^{\Delta\Delta}$
3 min	415 ± 23	414 ± 31	350 ± 43**$^{\Delta}$	355 ± 19**$^{\Delta\Delta}$
5 min	415 ± 26	415 ± 26	351 ± 47**$^{\Delta}$	358 ± 18**$^{\Delta\Delta}$
7 min	415 ± 29	413 ± 30	357 ± 41**$^{\Delta}$	367 ± 23*$^{\Delta\Delta}$
10 min	412 ± 28	409 ± 26	376 ± 54	378 ± 27$^{\Delta\Delta}$
15 min	413 ± 31	415 ± 26	384 ± 29	394 ± 27$^{\Delta\Delta}$
20 min	409 ± 26	413 ± 26	388 ± 47	385 ± 41$^{\Delta\Delta}$
25 min	409 ± 27	413 ± 30	394 ± 28	398 ± 19$^{\Delta\Delta}$
30 min	413 ± 29	413 ± 30	403 ± 49	405 ± 34

*P < 0.05, **P < 0.01 *vs*. the group C; $^{\Delta}P$ < 0.05, $^{\Delta\Delta}P$ < 0.01 *vs*. baseline.

Table 2. Effects of propofol on the LVSP in 30 min (n = 8, means ± SD)

Time	**LVSP** (mmHg)			
	Group C	Group I	Group P1	Group P2
Baseline	139 ± 10	143 ± 9	148 ± 31	144 ± 22
1 min	145 ± 8	142 ± 9	104 ± 26**$^{\Delta\Delta}$	84 ± 24**$^{\Delta\Delta}$
2 min	142 ± 9	139 ± 10	104 ± 26**$^{\Delta\Delta}$	94 ± 24**$^{\Delta\Delta}$
3 min	145 ± 7	145 ± 7	102 ± 40*$^{\Delta}$	101 ± 25*$^{\Delta\Delta}$
5 min	142 ± 8	145 ± 7	107 ± 36*$^{\Delta}$	107 ± 23*$^{\Delta\Delta}$
7 min	145 ± 7	142 ± 8	122 ± 20*	122 ± 19*
10 min	142 ± 8	142 ± 7	131 ± 35	131 ± 13
15 min	141 ± 8	143 ± 7	136 ± 32	124 ± 22
20 min	141 ± 8	146 ± 7	136 ± 32	131 ± 31
25 min	145 ± 8	144 ± 7	135 ± 23	134 ± 16
30 min	143 ± 9	146 ± 7	133 ± 30	129 ± 25

*P < 0.05, **P < 0.01 *vs*. the group C; $^{\Delta}P$ < 0.05, $^{\Delta\Delta}P$ < 0.01 *vs*. baseline.

rapid filtration under vacuum through glass fiber filters (GF/C Whatman, Clifton, NJ, USA). Each filter was then washed twice with an additional 10 ml of ice-cold buffer. Radioactivity retained on the filter was determined by a gamma counter. In each experiment, nonspecific binding of 125 iodocyanopindolol was determined in the presence of 5 mM of L-propranolol hydrochloride. Specific binding was defined as the total radioactivity bound minus the nonspecific binding. All binding data were analyzed by a computerized, nonlinear, curve-fitting program (GraphPad, San Diego, CA, USA). The maximal number of binding sites (Bmax, expressed in fmol/mg of protein) and the equilibrium dissociation constant (Kd, expressed in nmol/ml) for the receptors were determined and analyzed by the specific bindings as described by Scatchard (13).

Statistical Analysis

All data are expressed as means ± S.D., and separate analyses were performed for each treatment group with a repeated-measures Analysis of variance (ANOVA). A multiple-comparison procedure with the Bonferroni test was used to determine the significance of differences between two groups if the equal variances assumed, and the Tamhane's T2 was used if the equal variances not assumed. All statistical analyses were performed with the SPSS 12.0 software (SPSS, Chicago, IL, USA). P < 0.05 was considered as statistically significant.

Results

Effects of Propofol on HR, LVSP and LVEDP in 30 Min

There was no significant difference in HR, LVSP and LVEDP between group C and group I during 30 min (P > 0.05), and no variations of these indicators were observed in these two groups before and after injection (P > 0.05). The results also revealed that after injection no significant difference in HR, LVSP and LVEDP was found between groups P1 and P2 (P > 0.05).

Compared with group C, injection of propofol decreased HR and LVSP significantly in 7 min in both groups P1 and P2 (P < 0.05), while no significant difference of LVEDP was found (P > 0.05).

Compared to the baseline, propofol decreased HR and LVSP significantly in both groups P1 and P2 (P < 0.05), whereas no significant difference of LVEDP was found.

The above results are shown in Tables 1, 2 and 3 respectively.

Effects of Propofol on +dp/dt$_{max}$ in 30 Min

There was no significant difference in +dp/dt$_{max}$ and −dp/dt$_{max}$ between group C and group I during 30 min (P > 0.05).

Compared with group C, injection of both 5 mg/kg (group P1) and 10 mg/kg (group P2) propofol decreased +dp/dt$_{max}$ and −dp/dt$_{max}$ significantly in 7 min (P < 0.05).

There was no significant difference in +dp/dt$_{max}$ and −dp/dt$_{max}$ in groups C and I before and after injection for 30 min (P > 0.05), while in both groups P1 and P2, +dp/dt$_{max}$ and −dp/dt$_{max}$ were found up-regulated significantly after injection for 30 and 7 min respectively (P < 0.05). Compared to the baseline, injection of propofol at 5 mg/kg and 10 mg/kg

Table 3. Effects of propofol on the LVEDP in 30 min (n = 8, means ± SD)

Time	**LVEDP** (mmHg)			
	Group C	Group I	Group P1	Group P2
Baseline	3.9 ± 2.2	4.2 ± 2.5	4.7 ± 2.1	4.2 ± 2.7
1 min	3.8 ± 2.1	3.9 ± 2.8	4.6 ± 3.2	3.7 ± 2.9
2 min	3.9 ± 2.1	4.2 ± 2.9	3.7 ± 2.5	4.2 ± 2.5
3 min	3.5 ± 2.0	3.7 ± 3.0	3.8 ± 3.1	5.8 ± 3.6
5 min	3.4 ± 2.4	4.0 ± 2.9	3.6 ± 1.9	4.3 ± 4.5
7 min	3.6 ± 2.0	3.6 ± 2.7	4.0 ± 2.8	3.7 ± 3.0
10 min	3.9 ± 2.8	3.6 ± 2.8	2.9 ± 1.3	4.9 ± 4.0
15 min	3.8 ± 2.6	3.5 ± 2.7	3.2 ± 2.5	4.0 ± 3.0
20 min	3.9 ± 2.7	3.2 ± 2.9	2.7 ± 1.8	4.7 ± 3.5
25 min	3.9 ± 2.6	2.9 ± 2.8	3.4 ± 2.9	2.9 ± 2.2
30 min	4.1 ± 2.7	3.1 ± 2.5	3.2 ± 1.7	2.2 ± 2.0

Table 4. Effects of propofol on the +dp/dt$_{max}$ in 30 min (n = 8, means ± SD)

Time	**+d*p*/d*t*$_{max}$ (mmHg/S × 1000)**			
	Group C	Group I	Group P1	Group P2
Baseline	6.7 ± 1.5	6.7 ± 1.5	6.7 ± 1.4	6.7 ± 0.9
1 min	6.7 ± 1.5	6.8 ± 1.4	4.7 ± 0.8$^{**\Delta\Delta}$	4.5 ± 0.7$^{**\Delta\Delta}$
2 min	6.7 ± 1.5	6.7 ± 1.3	5.0 ± 1.1$^{*\Delta}$	4.2 ± 1.1$^{**\Delta\Delta}$
3 min	6.7 ± 1.5	6.8 ± 1.0	4.8 ± 1.5$^{*\Delta}$	4.6 ± 1.0$^{*\Delta\Delta}$
5 min	6.7 ± 1.5	6.7 ± 1.4	4.9 ± 1.4$^{*\Delta}$	5.1 ± 0.6$^{*\Delta\Delta}$
7 min	6.7 ± 1.6	6.6 ± 1.4	4.8 ± 0.5$^{**\Delta}$	4.6 ± 1.0$^{*\Delta\Delta}$
10 min	6.6 ± 1.5	6.8 ± 1.4	5.6 ± 1.4	5.2 ± 0.9$^{\Delta\Delta}$
15 min	6.6 ± 1.5	7.0 ± 1.2	5.5 ± 0.5$^{\Delta}$	5.5 ± 1.0$^{\Delta\Delta}$
20 min	6.6 ± 1.5	6.6 ± 1.5	5.2 ± 1.1$^{\Delta}$	5.4 ± 1.1$^{\Delta\Delta}$
25 min	6.7 ± 1.6	6.6 ± 1.8	5.4 ± 1.1$^{\Delta}$	5.6 ± 1.2$^{\Delta\Delta}$
30 min	6.6 ± 1.5	6.8 ± 1.4	5.3 ± 1.1$^{\Delta}$	5.5 ± 1.1$^{\Delta\Delta}$

*P < 0.05, **P < 0.01 *vs*. the group C; $^{\Delta}P$ < 0.05, $^{\Delta\Delta}P$ < 0.01 *vs*. baseline.

caused +dp/dt$_{max}$ to decrease significantly in 30 min in groups P1 and P2 (P < 0.05). As shown in Tables 4 and 5, the results also revealed no significant difference of +dp/dt$_{max}$ and –dp/dt$_{max}$ between groups P1 and P2 after injection for 30 min (P > 0.05).

Effects of Propofol on Bmax and Kd Value in 30 Min

After injection for 30 min, Bmax was found to increase significantly in both groups P1 and P2 (P < 0.05), while no significant difference was observed in groups C and I (P > 0.05).

Interestingly, the Kd value was found to increase only in group P2 after injection of propofol at 10 mg/kg for 30 min, while no significant difference was observed among other groups after injection for 30 min. As shown in Table 6, there was also no significant difference between groups P1 and P2 after injection for 3 and 10 min.

Table 5. Effects of propofol on the –dp/dt$_{max}$ in 30 min (n = 8, means ± SD)

Time	–dp/dt$_{max}$ (mmHg/s × 1000)			
	Group C	Group I	Group P1	Group P2
Baseline	6.1 ± 1.0	6.0 ± 1.0	6.1 ± 1.4	6.0 ± 1.5
1 min	6.0 ± 1.0	6.1 ± 1.0	4.4 ± 1.0$^{**\Delta\Delta}$	3.6 ± 0.6$^{**\Delta\Delta}$
2 min	6.0 ± 0.9	6.1 ± 0.9	4.4 ± 1.0$^{*\Delta}$	3.2 ± 1.0$^{**\Delta\Delta}$
3 min	6.1 ± 1.0	6.1 ± 1.0	4.2 ± 1.3$^{*\Delta}$	3.8 ± 1.0$^{**\Delta}$
5 min	6.0 ± 0.9	6.2 ± 0.9	4.5 ± 1.2$^{*\Delta}$	4.3 ± 0.4$^{**\Delta}$
7 min	6.0 ± 1.0	6.1 ± 1.0	4.3 ± 0.3$^{**\Delta\Delta}$	4.8 ± 1.0$^{*\Delta}$
10 min	6.0 ± 0.9	6.1 ± 1.0	5.0 ± 1.1	5.4 ± 1.0
15 min	6.0 ± 0.9	6.1 ± 1.0	4.8 ± 0.4	5.7 ± 1.2
20 min	6.1 ± 0.8	6.0 ± 1.0	5.2 ± 1.2	5.2 ± 1.5
25 min	6.0 ± 1.0	6.0 ± 1.0	4.9 ± 0.2	5.4 ± 1.4
30 min	6.1 ± 0.9	6.1 ± 1.0	5.3 ± 0.9	5.6 ± 1.1

*P < 0.05, **P < 0.01 *vs*. the group C; $^{\Delta}P$ < 0.05, $^{\Delta\Delta}P$ < 0.01 *vs*. baseline.

Table 6. Effects of propofol on the β-adrenoceptor in 30 min (n = 6, means ± SD)

	Group	3 min	10 min	30 min
Bmax (fmol/mg Pro)	C	1.6 ± 0.3	1.7 ± 0.4	1.5 ± 0.3
	I	1.5 ± 0.2	1.5 ± 0.3	1.3 ± 0.2
	P1	5.4 ± 1.3$^{**\#\#}$	9.8 ± 1.6$^{**\#\#}$	5.2 ± 0.9$^{**\#\#}$
	P2	6.0 ± 1.0$^{**\#\#}$	8.1 ± 2.8$^{*\#}$	7.6 ± 1.4$^{**\#\#}$
Kd (nmol/L)	C	1.3 ± 0.4	1.3 ± 0.5	1.2 ± 0.5
	I	1.3 ± 0.8	1.0 ± 0.5	1.7 ± 0.5
	P1	1.5 ± 0.2	1.5 ± 0.3	1.5 ± 0.2
	P2	2.9 ± 1.2$^{*\#\star}$	2.8 ± 1.2$^{*\#\star}$	3.0 ± 0.7$^{*\#\star}$

*P < 0.05, **P < 0.01 *vs*. the group C; $^{\#}P$ < 0.05, $^{\#\#}P$ < 0.01 *vs*. the group I; $^{\star}P$ < 0.05 *vs*. group P1.

Discussion

Propofol is a potent intravenous anesthetic and is insoluble in aqueous media. The distribution half-life of propofol is 2 to 4 min, and the elimination half-life is about 30 min, so we observed the left ventricular function for 30 min and observed myocardial β-adrenoceptor density and Kd value after propofol injection for 3, 10 and 30 min. The required induction dose and blood concentration of propofol are known to be species dependent, and for rats the required induction dose is 9.3 mg/kg (2). In this study, the propofol doses were selected according to a previous report (1). +dp/dt$_{max}$ represents the cardiac contractility, –dp/dt$_{max}$ represents ventricular diastole function and cardiac compliance, LVSP represents left ventricular pressure during systole, and LVEDP

represents end-diastolic pressure during diastole. The parameters sensitively resembled the left ventricular function.

There are a number of mechanisms concerning cardiovascular depression effects of propofol, such as inhibition of sympathetic nerve (12) and inhibition of calcium ion channel (6). Previous studies have shown that propofol may depress cardiac function by reduction in arterial blood pressure rather than by reduction in myocardial contractility (17). Most studies have reported that propofol may induce cardiovascular inhibition by monitoring noninvasive or invasive blood pressure, or by monitoring noninvasive cardiac function (7, 11, 16).

Myocardial β-adrenoceptors have the positive inotropic response and chronotropic sensitivity to regulate the cardiac function. Kurokawa *et al*. (5) reported that clinically relevant concentrations of propofol could attenuate beta-adrenergic signal transduction in cardiac myocytes *via* inhibition of cAMP production in *in vitro* experiments of freshly isolated ventricular myocytes. Zhou *et al*. (18) reported that 200 μM propofol would decrease cardiac β-adrenoceptor responsiveness in an *in vitro* study. The findings suggest that propofol inhibits cardiac function via the changed myocardial β-adrenergic receptor density, and its action contributes to the cardiovascular depression.

Most of the above studies were performed *in vitro*, and the results between *in vitro* and *in vivo* situations might be different so we focused on the effects in *in vivo* studies. In this study, our results showed significant downregulation of HR, LVSP, $+dp/dt_{max}$ and $-dp/dt_{max}$ after intravenous injection of different doses of propofol, and Bmax was remarkably upregulated concurrently after propofol injection for 30 min. Furthermore, our results also demonstrated that Kd value could be upregulated only in higher-dose bolus injection of propofol (10 mg/kg) for 30 min, while no significant variation occurred in lower-dose injection, or when the duration after injection of propofol was less than 30 min. We, therefore, conclude that intravenous injection of propofol bolus can inhibit the cardiac function partially *via* upregulation of Bmax and downregulation of the β-AR affinity at higher-dose injection of propofol bolus.

Under physiological conditions, cardiac β-ARs are distributed in the sarcolemmal membranes and the light vesicles, and the distribution of β-ARs in the heart can be altered under certain pathological conditions (14). Though many studies tried to explain why the distribution of β-ARs and the affinity in the heart can be altered under certain pathological conditions, the exact mechanism is unknown. Previous studies concluded that phosphorylation externalized β-adrenergic receptor from light vesicles to sarcolemma, and dephosphorylation internalized β-adrenergic receptor from sarcolemma to light vesicles (14). The desensitized β-ARs were associated with the phosphorylation of G-protein receptor kinase (15). The mechanism why propofol increased β-ARs density and decreased affinity in our study was unknown, and this needs further investigation.

Our results were different to the reports that propofol could downregulate Bmax *in vitro* (18). Many factors such as changes in heart rate, preload, afterload, oxygen demand, and central nervous system activity may affect the results of propofol *i.v.* bolus *in vivo* experiments (8). This may explain why the results of *in vivo* and *in vitro* experiments are different.

In conclusion, intravenous injection of propofol bolus may depress cardiac functions *via* upregulation of Bmax and downregulation of the β-AR affinity at higher-dose injection.

References

1. Bielen, S.J., Lysko, G.S. and Gough, W.B. The effect of a cyclodextrin vehicle on the cardiovascular profile of propofol in rats. *Anesth. Analg*. 82: 920-924, 1996.
2. Cockshott, I.D., Douglas, E.J., Plummer, G.F. and Simons, P.J. The pharmacokinetics of propofol in laboratory animals. *Xenobiotica* 22: 369-375, 1992.
3. Feldman, R.D., Limbird, L.E., Nadeau, J., Fitzgerald, G.A., Robertson, D. and Wood, A.J.J. Dynamic regulation of leukocyte beta adrenergic receptor agonist interactions by physiological changes in circulating catecholamines. *J. Clin. Invest*. 72: 164-170, 1983.
4. Foex, P., Diedericks, J. and Sear, J.W. Cardiovascular effects of propofol. *J. Drug Dev*. 4: 3-9, 1991.
5. Kurokawa, H., Murray, P.A. and Damron, D.S. Propofol attenuates beta-adrenoreceptor-mediated signal transduction *via* a protein kinase C-dependent pathway in cardiomyocytes. *Anesthesiology* 96: 688-698, 2002.
6. Kuusela, E., Vainio, O., Short, C.E., Leppaluoto, J., Huttunen, P., Strom, S., Huju, V., Valtonen, A. and Raekallio, M. A comparison of propofol infusion and propofol/isoflurane anaesthesia in dexmedetomidine premedicated dogs. *J. Vet. Pharmacol. Ther*. 26: 199-204, 2003.
7. Larsen, J.R., Torp, P., Norrild, K. and Sloth, E. Propofol reduces tissue-Doppler markers of left ventricle function: a transthoracic echocardiographic study. *Br. J. Anaesth*. 98: 183-188, 2007.
8. Lejay, M., Hanouz, J.L., Lecarpentier, Y., Coriat, P. and Riou, B. Modifications of the inotropic responses to alpha- and beta-adrenoceptor stimulation by propofol in rat myocardium. *Anesth. Analg*. 87: 277-283, 1998.
9. Lowry, O.H., Rosebrough, N.J. and Farr, A.L. Protein measurement with folin phenol reagent. *J. Biol. Chem*. 193: 265-275, 1951.
10. Nimmo, G.R., Mackenzie, S.J. and Grant, I.S. Hemodynamic and oxygen transport effects of propofol infusion in critically ill adults. *Anaesthesia* 4: 485-489, 1994.
11. Niwa, H., Tanimoto, A., Sugimura, M., Morimoto, Y. and Hanamoto, H. Cardiovascular effects of epinephrine under sedation with nitrous oxide, propofol, or midazolam. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod*. 102: e1-e9, 2006.
12. Puttick, R.M. and Terrar, D.A. Differential effects of propofol and enflurane on contraction dependent on calcium derived from the sarcoplasmic reticulum of guinea pig isolated papillary muscles. *Anesth. Analg*. 77: 55-60, 1993.

13. Scatchard, G. The attractions of proteins for small molecules and ions. *Ann. NY. Acad. Sci. USA*. 51: 660-672, 1972.
14. Tang, C. and Liu, M.-S. Internal externalization followed by internalization of β-adrenergic receptors in rat heart during sepsis. *Am. J. Physiol. Regul. Integr. Comp. Physiol*. 270: R254-R263, 1996.
15. Tang, C., Yang, J., Wu, L.L., Dong, L.W. and Liu, M.S. Phosphorylation of β-adrenergic receptor leads to its redistribution in rat heart during sepsis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 274: R1078-R1086, 1998.
16. Upton, R.N. and Ludbrook, G. A physiologically based, recirculatory model of the kinetics and dynamics of propofol in man. *Anesthesology* 103: 344-352, 2005.
17. Zheng, D., Upton, R.N. and Martinez, A.M. The contribution of the coronary concentrations of propofol to its cardiovascular effects in anesthetized sheep. *Anesth. Analg*. 96: 1589-1597, 2003.
18. Zhou, W., Fontenot, H.J., Wang, S.N. and Kennedy, R.H. Propofol-induced alterations in myocardial beta-adrenoceptor binding and responsiveness. *Anesth. Analg*. 89: 604-608, 1999.