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Propofol-induced Increase in Vascular Capacitance Is Due to Inhibition of Sympathetic Vasoconstrictive Activity

Sumio Hoka, M.D., Ken Yamaura, M.D.,† Tomoaki Takenaka, M.D.,‡ Shosuke Takahashi, M.D.§*

Background: **Venodilation is thought to be one of the mechanisms underlying propofol-induced hypotension. The purpose of this study is to test two hypotheses: (1) propofol increases systemic vascular capacitance, and (2) the capacitance change produced by propofol is a result of an inhibition of sympathetic vasoconstrictor activity.**

Methods: **In 33 Wistar rats previously anesthetized with urethane and ketamine, vascular capacitance was examined before and after propofol infusion by measuring mean circulatory filling pressure (P_{mcf}). The P_{mcf} was measured during a brief period of circulatory arrest produced by inflating an indwelling balloon in the right atrium. Rats were assigned into four groups: an intact group, a sympathetic nervous system (SNS)-block group produced by hexamethonium infusion, a SNS-block + noradrenaline (NA) group, and a hypovolemic group. The P_{mcf} was measured at a control state and 2 min after a bolus administration of 2, 10, and 20 mg/kg of propofol.**

Results: **The mean arterial pressure (MAP) was decreased by propofol dose-dependently in intact, hypovolemic, and SNS-block groups, but the decrease in MAP was less in the SNS-block group (−25%) than in the intact (−50%) and hypovolemic (−61%) groups. In the SNS-block + NA group, MAP decreased only at 20 mg/kg of propofol (−18%). The P_{mcf} decreased in intact and hypovolemic groups in a dose-dependent fashion but was unchanged in the SNS-block and SNS-block + NA groups.**

Conclusions: **The results have provided two principal findings: (1) propofol decreases P_{mcf} dose-dependently, and (2) the decrease in P_{mcf} by propofol is elicited only when the sympathetic nervous system is intact, suggesting that propofol increases systemic vascular capacitance as a result of an inhibition of sympathetic nervous system. (Key words: Hypovolemia; intravenous anesthetic; venous return.).**

PROPOFOL has been shown to cause systemic hypotension.[1,2] The precise mechanism of this hemodynamic response remains unclear despite several clinical and experimental studies.[3–5] Various postulated mechanisms for propofol-induced hemodynamic instability include a reduction in myocardial contraction, alterations in loading conditions, and changes in the central nervous system.[3–12]

Venodilation is thought to be one of the mechanisms underlying propofol-induced hypotension.[6–10] Several studies in humans have demonstrated a large decrease in cardiac filling pressure during the administration of propofol.[9,10] In *in vitro* studies, propofol also caused a direct relaxation of veins and arteries.[13] It has also been suggested that a direct vasodilation of venous smooth muscle may contribute to the propofol-induced hypotension in an *in vivo* animal study.[6] On the other hand, Robinson *et al.*[8] have demonstrated that the effect of propofol on forearm vein compliance was similar to the effect of sympathetic denervation by stellate ganglion blockade, concluding that an increase in venous compliance is primarily a result of an inhibition of sympathetic vasoconstrictor nerve activity.

Venous tones in different vascular beds are regulated in different ways depending on their nature.[14,15] Cutaneous venous tone is regulated by the thermoregulatory system. Skeletal veins play an important role, especially during exercise, as a muscle pump. Splanchnic venous tone largely contributes to a mobilization of blood volume by sympathetic nerve stimulation.[15–17] Total vascular capacitance, which is the relationship between contained volume and distending pressure of systemic vasculature, is a major factor influencing filling of the

* Professor of Anesthesiology, Kitasato University.

† Instructor of Anesthesiology, Kyushu University.

‡ Lecturer of Anesthesiology, Kitasato University.

§ Professor of Anesthesiology, Kyushu University.

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Address reprint requests to Dr. Hoka: Department of Anesthesiology, Kitasato University, School of Medicine, 1-15-1 Kitasato, Sagamihara, Kanagawa 228, Japan. Address electronic mail to: shoka@med.kitasato-u.ac.jp

right heart and therefore has a critical effect on cardiac output.[15–17]

This study tests two hypotheses: (1) propofol increases systemic vascular capacitance, and (2) the capacitance change produced by propofol is a result of inhibition of sympathetic vasoconstrictor activity. An alteration in systemic vascular capacitance can be assessed by measuring mean circulatory filling pressure (P_{mcf}).[15–18] We examined the effect of propofol on P_{mcf} in intact and sympathetically denervated rats.

Methods

Thirty-three Wistar rats, weighing 300–400 g, were used for this experiment under the approval of the our institutional Animal Care Committee. The rat was initially anesthetized with urethane (1 g/kg) and ketamine (100 mg/kg) intraperitoneally, and then tracheostomy was done. The rat was mechanically ventilated using a Harvard respirator (Harvard Apparatus, MA) with oxygen to maintain Pa_{O_2} and Pa_{CO_2} at physiologic levels. Two catheters (Argyle 20-gauge, Nippon Sherwood, Tokyo, Japan) were placed in the left femoral artery and vein and connected to pressure transducers for recording arterial and central venous pressure, respectively. The arterial catheter was advanced to iliac bifurcation, and the venous catheter was positioned in the abdominal inferior vena cava. The proper position of venous catheter was confirmed by a synchronous change of the venous pressure with respiration. A balloon-tipped catheter was placed in the right atrium through the right external jugular vein, and the proper location was tested by injecting 0.3 ml of air into the balloon to stop the circulation completely. If the characteristic smooth increase in venous pressure and simultaneous decrease in arterial pressure to less than 35 mmHg were not observed, the balloon was repositioned. The right femoral vein was also cannulated (Argyle 20-gauge, Nippon Sherwood) and used for a drug infusion route. Body temperature was maintained by a heating pad and a heating lamp.

Measurement of Mean Circulatory Filling Pressure

Mean circulatory filling pressure was measured by the method introduced by Yamamoto *et al.*[19] Immediately after the balloon was inflated, arterial pressure decreased, and venous pressure increased simultaneously. Central venous pressure reached a plateau within 4–5 s. Because arterial and venous pressures during circulatory arrest were not in complete equilibrium, P_{mcf} was calculated according to the following equation:

$$P_{mcf} = VPP + K\ (FAP - VPP)$$

where VPP is the venous plateau pressure; FAP is the final arterial pressure, and K is the ratio of the arterial-to-venous compliance. Accordingly to the report by Yamamoto *et al.*,[19] a K value of 1/60 was used in this experiment. Measurements of P_{mcf} began about 30 min after ketamine administration.

Response to Propofol

Twenty-eight rats were assigned into four groups: intact (n = 8), sympathetic nervous system (SNS)-block (n = 6), SNS-block + noradrenaline (NA) (n = 9), and hypovolemic (n = 5) groups. SNS-block was performed with intravenous administration of ganglionic blockade hexamethonium (10 mg/kg), and NA was infused continuously to restore mean arterial pressure (MAP) toward the baseline level just before hexamethonium administration in SNS-block + NA groups. Hypovolemia was produced by 10 ml/kg of hemorrhage. P_{mcf} was measured at the control state and 2 min after the bolus administration of 2, 10, and 20 mg/kg of propofol. Propofol was administered after at least a 20-min interval in a cumulative fashion.

Response to Trinitroglycerin

To examine whether a direct venodilator activity is elicited in sympathetically blocked rats, trinitroglycerin (TNG) was administered in another five rats from the intact, SNS-block, and SNS-block + NA groups. P_{mcf} was measured after 1–2 min after a bolus administration of TNG 200 μg/kg, which caused a decrease in MAP of approximately 20–30 mmHg.

Statistical Analysis

Results are expressed as mean ± SEM. The effects of group treatments on hemodynamics in comparison with the baseline values were analyzed using paired Student's *t* test. The significance of differences between groups and the significance of changes at different propofol doses were assessed by the analysis of variance (ANOVA) with repeated measures. When the ANOVA demonstrated significant differences, the unpaired Student's *t* test was used to compare groups at equivalent doses. The comparisons within groups to assess changes from the control value were analyzed with the paired Student's *t* test with Bonferroni's correction.

Table 1. Mean Arterial Pressure (MAP), Heart Rate (HR), Central Venous Pressure (CVP), Final Arterial Pressure (FAP), Venous Plateau Pressure (VPP), and Mean Circulatory Filling Pressure (Pmcf) at the Baseline and After Treatment in Four Groups

	MAP	HR	CVP	FAP	VPP	Pmcf
Intact group	114 ± 5	396 ± 17	2.4 ± 0.2	28 ± 3	7.3 ± 0.4	7.6 ± 0.4
SNS block group						
Baseline	102 ± 4	396 ± 4	2.7 ± 0.3	29 ± 7	6.9 ± 0.4	7.3 ± 0.4
After Hex	64 ± 5*	377 ± 12	2.7 ± 0.2	24 ± 4	5.3 ± 0.4*	5.6 ± 0.3*
SNS block + NA group						
Baseline	105 ± 3	389 ± 13	2.7 ± 0.2	29 ± 5	6.8 ± 0.3	7.2 ± 0.3
After Hex + NA	104 ± 3	393 ± 20	2.7 ± 0.2	28 ± 3	7.6 ± 0.3*	8.0 ± 0.3*
Hypovolemia group						
Baseline	110 ± 4	411 ± 7	2.7 ± 0.3	25 ± 4	7.3 ± 0.4	7.6 ± 0.4
After hemorrhage	96 ± 5*	412 ± 11	2.7 ± 0.5	24 ± 3	6.1 ± 0.3*	6.4 ± 0.4*

SNS = sympathetic nervous system; Hex = hexamethonium; NA = noradrenaline.

* $P < 0.05$ *versus* baseline.

Results

Table 1 summarizes values for MAP, heart rate, central venous pressure, final arterial pressure, venous plateau pressure, and P_{mcf} at the baseline and after treatment in four groups. SNS-block decreased MAP approximately by 40%, whereas SNS-block + NA reversed MAP similar to the baseline level. The dosage of NA administered was 1.50 ± 0.33 $\mu g \cdot min^{-1} \cdot kg^{-1}$. Hypovolemia of 10 ml/kg decreased MAP approximately by 15%. P_{mcf} was decreased by SNS-block and hypovolemia, whereas SNS block + NA reversed P_{mcf} to a slightly but significantly higher level than the baseline level.

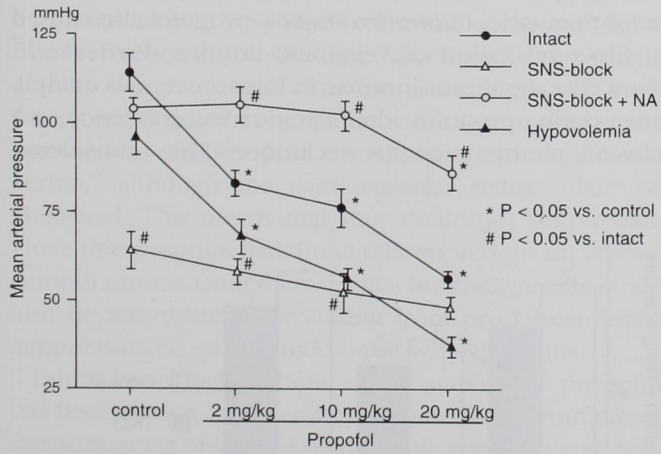

Fig. 1. Changes in MAP (mean arterial pressure) in association with infusions of propofol. The MAP was decreased by propofol dose-dependently in intact and hypovolemic groups. In the SNS-block group, MAP tended to decrease but not significantly different from the control group. In SNS-block + NA group, MAP decreased only at 20 mg/kg of propofol (−18%). SNS-block was performed by hexamethonium (10 mg/kg) infusion. Hypovolemia was produced by hemorrhage of 10 ml/kg. SNS = sympathetic nervous system; NA = noradrenaline.

Figure 1 shows changes in MAP by infusions of propofol. The MAP was decreased by propofol dose-dependently in intact and hypovolemic groups. In the SNS-block group, MAP tended to decrease but not significantly from the control group. In the SNS-block + NA group, MAP decreased only at 20 mg/kg of propofol.

Figure 2 shows changes in heart rate in four groups by infusions of propofol. Propofol slightly decreased the heart rate in all four groups.

Figure 3 shows changes in P_{mcf} in four groups by infusions of propofol. P_{mcf} decreased in the intact and hypovolemic groups but was unchanged in SNS-block. In the SNS-block plus NA group, P_{mcf} did not change at 2

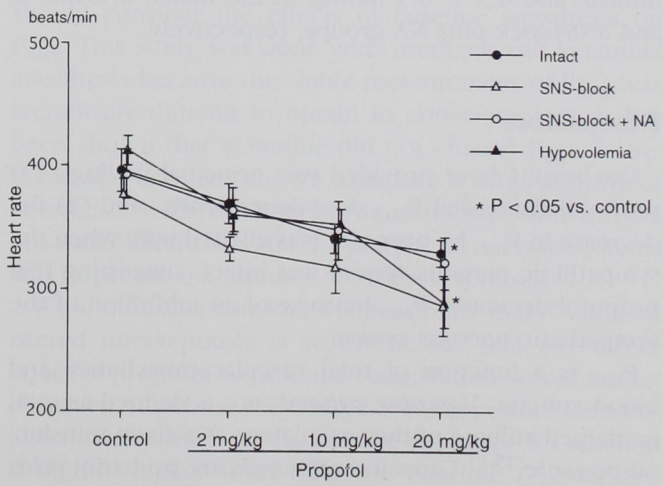

Fig. 2. Changes in heart rate in association with infusions of propofol. Propofol slightly decreased heart rate similarly in all four groups. SNS-block was performed by hexamethonium (10 mg/kg) infusion. Hypovolemia was produced by hemorrhage of 10 ml/kg. SNS = sympathetic nervous system; NA = noradrenaline.

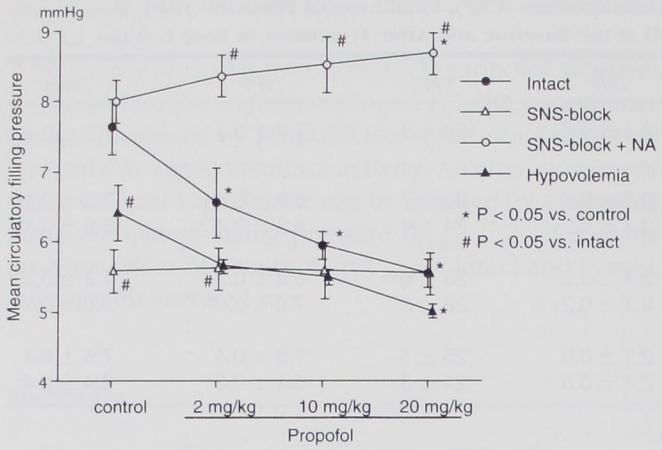

Fig. 3. Changes in P_{mcf} (mean circulatory filling pressure) in four groups by infusions of propofol. P_{mcf} decreased in the intact and hypovolemic groups but was unchanged in the SNS-block and SNS-block + NA groups. SNS-block was performed by hexamethonium (10 mg/kg) infusion. Hypovolemia was produced by hemorrhage of 10 ml/kg. SNS = sympathetic nervous system; NA = noradrenaline.

and 10 mg/kg of propofol, whereas it increased slightly at 20 mg/kg of propofol.

Figure 4 shows the effect of TNG on P_{mcf} at three conditions of intact, SNS-block, and SNS-block plus NA. TNG decreased MAP from 95 ± 10 mmHg to 71 ± 4 mmHg, from 79 ± 4 mmHg to 61 ± 11 mmHg, and from 104 ± 11 mmHg to 76 ± 7 mmHg in the intact, SNS-block, and SNS-block plus NA groups, respectively. TNG significantly reduced P_{mcf} by 1.2 ± 0.4 mmHg, 0.7 ± 0.4 mmHg, and 0.9 ± 0.5 mmHg in the intact, SNS-block, and SNS-block plus NA groups, respectively.

Discussion

Our results have provided two principal findings: (1) propofol decreased P_{mcf} dose-dependently, and (2) the decrease in P_{mcf} by propofol was elicited only when the sympathetic nervous system was intact, suggesting that propofol decreases P_{mcf} because of an inhibition of the sympathetic nervous system.

P_{mcf} is a function of total vascular capacitance and blood volume. *Vascular capacitance* is defined as total contained volume of the vasculature at a given transmural pressure.[15,17] Capacitance vessels are primarily veins and venules. If blood volume is constant, the P_{mcf} change reflects mostly alteration of venous rather than arterial tone. Therefore, our results suggest that propofol causes venodilation in a dose-dependent fashion and that the propofol-induced decrease in venous tone is primarily the result of an inhibition of sympathetic vasoconstrictor activity. This depressant effect of propofol on P_{mcf} and thus venous tone may contribute to decreasing venous return and cardiac output because venous return to the heart is proportional to the difference between the P_{mcf} and right atrial pressure. The decrease in P_{mcf} was prominent in hypovolemic rats, suggesting that the influence of propofol-induced decrease in venous tone may be exaggerated in a hypovolemic condition where the sympathetic nervous system contributes to the circulatory compensation.

The validity of this method for the measurements of P_{mcf} has been discussed in the previous reports.[19,20] It has been shown that P_{mcf} obtained by this method is not different from P_{mcf} obtained by the classical method[21] using blood transfer from the arterial to venous system after circulatory arrest.[19] A number of studies examining the effect of various vasoactive drugs[22–24] or anesthetic agents[20] on vascular capacitance have used this method.

Several previous studies have investigated the influence of propofol administration on the venous system or the capacitance properties of circulation. Goodchild and Serrao[6] estimated changes in capacitance by quantitating the amount of intravenous volume necessary to maintain venous pressure and pulmonary artery occlusion pressure at control values during propofol administration in chloralose-anesthetized dogs in which all neurogenic cardiovascular reflexes were abolished. They concluded that propofol had direct dilating actions on venous smooth muscle. In *in vitro* studies, propofol also caused a direct relaxation of veins and arteries. Muzi *et al.*[7] showed a significant increase in forearm venous compliance during propofol administration using a venous occlusion plethysmography technique. They considered

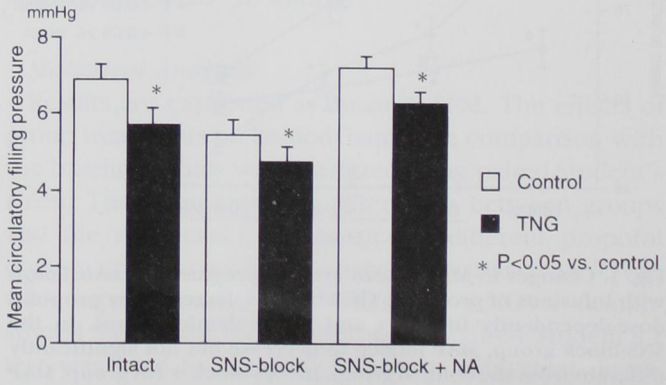

Fig. 4. The effects of TNG (trinitroglycerin) on P_{mcf} (mean circulatory filling pressure) at intact and after SNS-block and SNS-block + NA. TNG significantly reduced P_{mcf} at these three conditions. SNS = sympathetic nervous system; NA = noradrenaline.

the effect of propofol on venous smooth muscle of the forearm as, for the most part, a direct action of propofol because forearm muscle veins appear to react minimally to sympathetic stimuli.[15,25]

Recently, however, Robinson *et al.*,[8] from the same laboratory as Muzi *et al.*,[7] have provided excellent results regarding the precise mechanisms of alteration of venous compliance during propofol infusion. Propofol infusions into the brachial artery caused no significant change in vascular response, and the effects of intravenous propofol anesthesia on forearm vein compliance were similar to the effects of sympathetic denervation by stellate ganglion blockade, leading to the conclusion that the peripheral vascular actions, including an increase in venous compliance, are primarily the result of an inhibition of sympathetic vasoconstrictor nerve activity. Their results are consistent with our results in terms of sympathetically mediated mechanisms of propofol-induced venodilation. The inconsistency of actions of propofol on peripheral vasculature with previous reports[6,13] may be a result of the difference of methods, larger drug concentration for *in vitro* studies, the difference of vascular beds chosen, the species difference, or misleading interpretation.

For example, Goodchild and Serrao[6] used bretylium tosylate and propranolol in combination with bilateral vagotomy and carotid ligatures to abolish neurogenic cardiovascular reflexes. However, bretylium tosylate could not suppress increase of systemic blood pressure and heart rate in response to carotid occlusion (fig. 4 from reference 26), indicating that efferent sympathetic activity was increased after bretylium tosylate. Therefore, it is unlikely that sympathetic outflow to the venous system was abolished in the study of Goodchild and Serrao,[6] although the cardiovascular reflex might be abolished. This means that they could not simply conclude that propofol had direct dilating actions on venous smooth muscle from their results, but their results could also be interpreted as resulting from propofol-induced suppression of sympathetic outflow to the veins.

Inhibition of sympathetic nerve activity by propofol has been shown by several investigators[11,12] from direct measurements of muscle sympathetic nerve activity. Sellgren *et al.*[12] found a decrease of 61% in total muscle sympathetic nerve activity after a bolus injection of propofol (2 mg/kg). Ebert *et al.*[11] also showed a significant decrease of muscle sympathetic nerve activity during induction of propofol anesthesia. On the other hand, it has also been shown that propofol did not prevent a sympathetic response to the stimulation that attends laryngoscopy and intubation or the stimulus provided by a rapid increase in desflurane concentration.[27,28]

Alterations of P_{mcf} and thus vascular capacitance in response to changes in sympathetic nerve activity can be produced by changes in stressed volume or vascular compliance.[15–18] Total blood volume is divided into stressed and unstressed volume.[15–18] The stressed volume is a hemodynamically active component of blood volume, which determines the venous pressure for venous return. A change in sympathetic nerve activity can primarily cause an alteration of stressed volume rather than venous compliance.[15–18] For example, intense neurogenic venoconstriction evoked by carotid sinus hypotension or noradrenaline increases stressed volume to a great extent but alters little venous compliance.[15–18] Constricted veins exhibit increased stressed volume, and dilated veins show the reverse. Therefore, it is suggested that propofol may decrease stressed volume and thus venous return.

We should consider the effects of fluid infusion on measurement of P_{mcf}. Propofol was given cumulatively by intravenous infusion so that the resulting increase in blood volume could have increased P_{mcf}. However, the P_{mcf} was decreased by propofol infusion in intact rats. Thus, it may be possible that the propofol-induced increase in vascular capacitance is somewhat underestimated by a slight increase of blood volume by propofol administration. The increase in P_{mcf} that was observed in SNS-block + NA rats at 20 mg/kg of propofol may be caused by this increase in blood volume. In addition, we should consider the effects of baseline anesthesia on P_{mcf}. This study was done with urethane and ketamine anesthesia because the stable measurement of P_{mcf} was technically difficult to obtain in conscious rats. It has been shown that ketamine did not change P_{mcf}.[20] Urethane also has been shown to induce a surgical plane of anesthesia without affecting neurotransmission in various subcortical areas and the peripheral nervous systems and to preserve a number of reflex responses.[29]

We should also consider the possibility that NA administered intravenously is so efficacious that any direct effect of propofol to produce venodilation would not be observed. We chose the dosage of NA to restore the MAP just at the baseline levels, but the P_{mcf} after NA reached a slightly higher level than the baseline (7.2 *vs.* 8.0 mmHg). However, this P_{mcf} (8 mmHg) in SNS-block + NA rats is not a high level that could overcome direct venodilation or venoconstriction. We demonstrated that TNG, a well-known venodilator agent, could reduce P_{mcf} even in the presence of a sympathectomy with or with-

out NA (fig. 4), suggesting that venodilating activity still remained in SNS-block + NA rats.

Our results showed that heart rate decreased in SNS-block and SNS-block + NA rats and in intact rats. Accordingly, a decrease in heart rate seems to be independent of sympathetic nerve activity, suggesting a direct negative chronotropic property of propofol.

In conclusion, propofol causes an increase in vascular capacitance by way of an inhibition of sympathetic nerve activity. An increase in vascular capacitance may contribute to significant hypotension during propofol infusion. In patients with hypovolemia, propofol may accelerate a decrease in venous return and thus a decrease in cardiac output. On the other hand, in patients with congestive heart failure, an increase in vascular capacitance by propofol may be beneficial to reduce the preload and lessen the cardiac work simultaneously with the reduction of afterload.

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