Anesthesiology
1997; 86:64-72
© 1997 American Society of Anesthesiologists, Inc.
Lippincott-Raven Publishers

Mechanisms whereby Propofol Mediates Peripheral Vasodilation in Humans

Sympathoinhibition or Direct Vascular Relaxation?

B. J. Robinson, Ph.D.,* T. J. Ebert, M.D., Ph.D.,† T. J. O'Brien, M.D.,‡ M. D. Colinco, M.D.,‡ M. Muzi, M.D.§

Background: **Anesthetic induction and maintenance with propofol are associated with decreased blood pressure that is, in part, due to decreased peripheral resistance. Several possible mechanisms whereby propofol could reduce peripheral resistance include a direct action of propofol on vascular smooth muscle, an inhibition of sympathetic activity to the vasculature, or both. This study examined these two possibilities in humans by measuring the forearm vascular responses to infusions of propofol into the brachial artery (study 1) and by determining the forearm arterial and venous responses to systemic (intravenous) infusions of propofol after sympathetic denervation of the forearm by stellate blockade (study 2).**

Methods: **Bilateral forearm venous occlusion plethysmography was used to examine forearm vascular resistance (FVR) and forearm vein compliance (FVC). Study 1 used infusion of intralipid (time control) and propofol at rates between 83 and 664 μg/min into the brachial artery of 11 conscious persons and compared responses to arterial infusions of sodium nitroprusside (SNP) at 0.3, 3.0, and 10 μg/min. Venous blood from the infusion arm was assayed for plasma propofol concentrations. In study 2, after left stellate block (12 ml 0.25% bupivacaine + 1% lidocaine), six participants were anesthetized and maintained with propofol infusions of 125 and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Simultaneous right forearm (unblocked) blood flow dynamics served as the time control. In three additional conscious participants, intrabrachial artery infusions of SNP and nitroglycerin, both at 10 μg/min, were performed before and after stellate blockade of the left forearm to determine whether the sympathetically denervated forearm vessels could dilate beyond the level produced by denervation alone.**

Results: **In study 1, infusion of intralipid or propofol into the brachial artery did not change FVR or FVC. Sodium nitroprusside significantly decreased FVR in a dose-dependent manner by 22 ± 5%, 65 ± 3%, and 78 ± 2% (mean ± SEM) but did not change FVC. During the incremental propofol infusions, plasma propofol concentrations increased from 0.2 to 10.1 μg/ml and averaged 7.4 ± 1.1 μg/ml during the highest infusion rate. In study 2, stellate ganglion blockade decreased FVR by 50 ± 6% and increased FVC by 58 ± 10%. Propofol anesthesia at 125 and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ progressively reduced mean arterial pressure. In the arm with sympathetic denervation, FVR and FVC showed no further changes during propofol anesthesia, whereas in the control arm FVR significantly decreased by 41 ± 9% and 42 ± 7%, and FVC increased significantly by 89 ± 27% and 85 ± 32% during 125 and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusions of propofol, respectively. In the three additional conscious participants, intraarterial infusion of SNP and nitroglycerin (TNG) after the stellate blockade resulted in a further decrease of FVR and a further increase of FVC.**

Conclusions: **In contrast to SNP infusions, propofol infusions into the brachial artery of conscious persons caused no significant vascular responses, despite the presence of therapeutic plasma concentrations of propofol within the forearm. The effects of propofol anesthesia on FVR and FVC are similar to the effects of sympathetic denervation by stellate ganglion blockade. Thus the peripheral vascular actions of propofol appear to be due primarily to an inhibition of sympathetic vasoconstrictor nerve activity. (Key words: Anesthetics, intravenous: propofol. Measurement techniques, plethysmography: forearm blood flow.)**

* Postdoctoral Fellow of Anesthesiology.

† Professor of Anesthesiology and Physiology.

‡ Senior Resident of Anesthesiology.

§ Assistant Professor of Anesthesiology.

Received from the Department of Anesthesiology, the Medical College of Wisconsin, and VA Medical Center, Milwaukee, Wisconsin. Submitted for publication May 2, 1996. Accepted for publication September 23, 1996. Supported in part by Zeneca Pharmaceuticals, the National Institutes of Health, and the VA Medical Center.

Address reprint requests to Dr. Ebert: Department of Anesthesiology, 112A, VA Medical Center, 5000 West National Avenue, Milwaukee, Wisconsin 53295.

INDUCTION and maintenance of anesthesia with propofol are associated with decreased arterial blood pressure. Several studies suggest that the mechanisms of hypotension are propofol-mediated decreases in preload, cardiac output, and contractility.[1,2] In contrast, other studies have reported propofol-mediated decreases in afterload and systemic vascular resistance.[3-8] We have previously described decreases in forearm vascular resistance (FVR) and increases in forearm venous compliance (FVC) during propofol anesthesia in humans.[9,10] These observations indicate that arteriolar and venous dilation contrib-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/86/1/64/365081/0000542-199701000-00010.pdf by guest on 10 April 2024

ute to the hypotension associated with propofol. The precise mechanism(s) that contributes to the decreased vascular resistance with propofol is unclear. We and others have reported that induction of anesthesia with propofol is associated with a sudden cessation of peripheral sympathetic (vasoconstrictor) nerve activity.[9,11-13] Therefore, vasodilation could be due to the inhibition of tonic or baroreflex control (or both) of sympathetic outflow and vasoconstriction. However, in animals, propofol has been shown to act directly on vascular smooth muscle. *In vitro* preparations of arteries and veins from rats, rabbits, and dogs show vasorelaxation when exposed to propofol, and the endogenous vasodilator nitric oxide may be involved in the response.[14-21] In addition, it appears that veins may be more sensitive than arteries to propofol.[14,19]

This study tests two hypotheses: first, that propofol has direct actions on peripheral blood vessels, and second, that the vascular effects of propofol are due, in part, to inhibition of peripheral sympathetic vasoconstrictor activity. Accordingly, the aim of the present investigations was to evaluate the contributions of propofol-mediated sympathetic inhibition and direct vascular relaxation that cause a decreased FVR and increased FVC in humans. In one study, participants received propofol by microinfusions of subhypnotic doses directly into the brachial artery. This *in situ* method allows therapeutic concentrations of propofol to be established within the arterial and venous beds of the forearm. Centrally mediated effects of propofol are minimized because the venous outflow from forearm arterial microinfusions are diluted within the total-body circulation and are rapidly metabolized and distributed. Measurements from the opposite forearm serve as a control. The arterial effects of propofol were compared with microinfusions of another arterial vasodilator, sodium nitroprusside (SNP).

In the second study, the left forearm was sympathetically denervated (by stellate ganglion blockade) to compare the forearm vascular effects of intravenous anesthetic (maintenance) doses of propofol with the responses in the unblocked forearm on the contralateral side. If propofol has direct vascular effects to produce vasodilation, then comparable decreases in FVR and increases in FVC should be observed in each forearm. Conversely, if the vascular effects of propofol are predominantly mediated by an inhibition of sympathetic vasoconstrictor outflow, the denervated forearm would show no further increase in blood flow during propofol anesthesia.

Materials and Methods

Study 1: Brachial Artery Infusion of Propofol

After the institutional research review board gave its approval, informed consent was obtained from 11 healthy persons (age: 21-29 years; weight: 61-82 kg; sex: nine men, two women) with no systemic illness and who were not taking prescription medications or illicit drugs. After local infiltration with 0.5 ml 1% lidocaine, a 20-gauge catheter was placed in the brachial artery of the study arm to infuse drugs and to measure mean arterial pressure. The other (noninfusion) arm served as the control and did not have an arterial catheter. Two 18-gauge catheters were placed in superficial veins of each forearm to measure venous blood pressure. The distal lumens of the catheters were positioned so that pressure would be sensed at the upper forearm in close proximity to the strain gauge used for plethysmography. Participants received sequential brachial artery infusions of saline, intralipid, and propofol (83, 166, 332, and 664 μg/min), and, after a 10-min recovery, SNP (0.3, 3, and 10 μg/min). Each infusion rate was 5 ml/min for 15 min. Measurements of forearm blood flow (FBF), FVC, and skin blood flow (SBF) were made during the last 5 min of each infusion. The propofol infusion rates were calculated to achieve plasma concentrations within the brachial arterial and forearm venous system similar to the reported therapeutic ranges of propofol (2-6 μg/ml).[22,23] Blood samples were drawn from the venous catheter of the infusion arm of six participants at the end of each propofol dose to determine plasma propofol concentrations. The SNP brachial artery infusion rates were chosen based on a previous study.[24]

Study 2: Propofol Anesthesia with Stellate Ganglion Blockade

After the institutional research review board gave its approval, informed consent was obtained from six healthy men (age: 19-25 years; weight: 64-84 kg) with no systemic illness and who were not taking prescription medications or illicit drugs. A 20-gauge catheter was placed in the radial artery of the right arm to measure mean arterial pressure. Two 18-gauge catheters were placed in superficial veins of each forearm to measure venous blood pressure, and an 18-gauge catheter was placed in a foot or ankle vein to administer saline solution and anesthetics. Skin temperature probes were placed on a finger tip of each hand. After baseline FVR, FVC, and SBF measurements were taken, left stellate

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/86/1/64/365081/0000542-199701000-00010.pdf by guest on 10 April 2024

ganglion blockade was performed (12 ml of 2% lidocaine and 0.125% bupivacaine injected at the C7 level). Left-sided stellate blocks were selected to avoid cardiac dysrhythmias that occur more frequently with right-sided stellate blockade.[25,26] Measurements of FVR, FVC, and SBF were repeated 15 minutes after the stellate blockade was performed. Adequacy of the stellate block was confirmed by an increase in the finger skin temperature to more than 34°C. Anesthesia was induced with 2.5 mg/kg propofol, and 0.1 mg/kg vecuronium was given. After tracheal intubation, the lungs were ventilated with 100% oxygen and normocarbia was maintained. Propofol anesthesia was maintained using infusion rates of 125 and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol, in random order. Twenty min after starting the propofol infusion or changing the propofol infusion rate, FBF, FVC, and SBF were recorded and an arterial blood sample was drawn to determine plasma propofol levels.

The Effect of Vasodilators and Stellate Ganglion Blockade

To determine whether the sympathetically denervated forearm vessels could dilate beyond the level produced by denervation alone, three additional participants (men, ages 20–31 y) were enrolled and forearm arterial and venous responses to incremental intrabrachial artery infusions of SNP (10 μg/min) and nitroglycerin (10 μg/min) were examined before and after stellate blockade of the left forearm. These persons also served to confirm the persistence of the sympathetic blockade for more than 1.5 h, thereby increasing the likelihood that the responses to propofol in study 2 reflect direct effects secondary to a maintained sympathetic block.

Forearm Vascular Measurements

Sequential determinations of FBF and FVC were made simultaneously in both forearms using venous occlusion plethysmography with mercury-in-Silastic strain gauges, a plethysmographic balancing system and amplifier, and a rapid cuff inflater (DE Hokanson, Issaquah, WA). These techniques have been described and reviewed elsewhere.[9,10,27] Briefly, both arms were elevated and passively supported above the height of the right atrium to ensure adequate venous drainage between measurements. Inflatable blood pressure cuffs were placed about both wrists and upper arms and a strain gauge was placed around each forearm at the region of greatest circumference. Forearm blood flow was measured by calculating the rate of the increase in forearm volume during inflation of the cuffs to 50 mmHg for 10-s peri-

Table 1. Changes from Saline Infusion in Forearm Vascular Resistance (FVR), Forearm Venous Compliance (FVC), and Skin Blood Flow (SBF) during Brachial Artery Infusions of Propofol and SNP

			Propofol Infusion Rate ($\mu g \cdot min^{-1}$) (or time control, no infusion)				SNP Infusion Rate ($\mu g \cdot min^{-1}$) (or time control, no infusion)		
	Saline Infusion	Intralipid	83	166	332	664	0.3	3.0	10.0
Change from saline infusion FVR ($mmHg \cdot ml^{-1} \cdot 100\ ml \cdot min$)	21 ± 2	0 ± 1	1 ± 1	3 ± 2	3 ± 1	2 ± 1	−7 ± 3*	−18 ± 2*	−21 ± 2*
FVC ($ml \cdot mmHg^{-1}$)	6.1 ± 0.9	0.2 ± 0.3	0.8 ± 0.6	0.5 ± 0.4	0.1 ± 0.3	0.2 ± 0.5	0.3 ± 0.3	−0.2 ± 0.3	−0.5 ± 0.3
SBF, infusion arm:noninfused arm ratio	1.13 ± 0.08	−0.06 ± 0.11	−0.03 ± 0.07	0.01 ± 0.01	−0.15 ± 0.07	−0.13 ± 0.07	0.16 ± 0.07	0.12 ± 0.08	0.03 ± 0.07

* $P < 0.0001$, significant change from saline infusion, ANOVA.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/86/1/64/365081/0000542-199701000-00010.pdf by guest on 10 April 2024

ods. Forearm vascular resistance was calculated by dividing mean arterial pressure by FBF. Forearm vascular compliance was derived by inflating the cuffs to 30 mmHg for an extended period until forearm vein pressure had stabilized. The change in forearm volume was measured 30 s after the plateau of venous pressure to increase the likelihood that both deep and superficial vein pressures had stabilized[28]; FVC was calculated by dividing the change in forearm volume by the change in venous pressure. Finger SBF was qualitatively measured as the pulse wave amplitude using infrared photoplethysmographic sensors (Grass Instruments, West Warwick, RI) that were applied to the middle fingers of both hands.[29] Pulse wave amplitudes were adjusted to be equal for both hands during baseline measurements. Relative skin vasodilation was expressed as the ratio of the pulse wave amplitudes of the treatment forearm (*i.e.,* brachial infusion or stellate blockade) to that of the control forearm; for example, a ratio more than 1 indicated SBF greater in the treatment forearm than in the control forearm.

Statistics

Data were analyzed using analysis of variance (Stat View 4.02; Abacus Concepts, Berkeley, CA) and $P < 0.05$ indicated statistical significance. Data are reported as mean ± SEM.

Results

Study 1: Brachial Artery Infusion of Propofol

None of the participants reported pain or discomfort during the brachial artery infusions of propofol. Data are summarized in table 1. Infusion of intralipid or propofol into the brachial artery did not change FVR, FVC, or SBF. Brachial artery infusions of 0.3, 3, and 10 μg/min SNP decreased FVR by (mean ± SEM) 7 ± 1, 18 ± 2, and 21 ± 2 mmHg · ml^{-1} · 100 ml/min^{-1}, respectively ($P < 0.0005$), but did not affect FVC. There were no significant changes in FVR or FVC in the control forearm. Figure 1 shows the percentage changes in FVR from saline infusions. There were no significant changes in the ratios of the photoplethysmographic wave amplitudes. Plasma propofol concentrations measured in forearm venous blood sampled during forearm arterial propofol infusions ranged from 0.2 to 10.1 μg/ml and were dose dependent (fig. 2). There were no significant correlations between plasma propofol concentrations and FVR, FVC, and SBF.

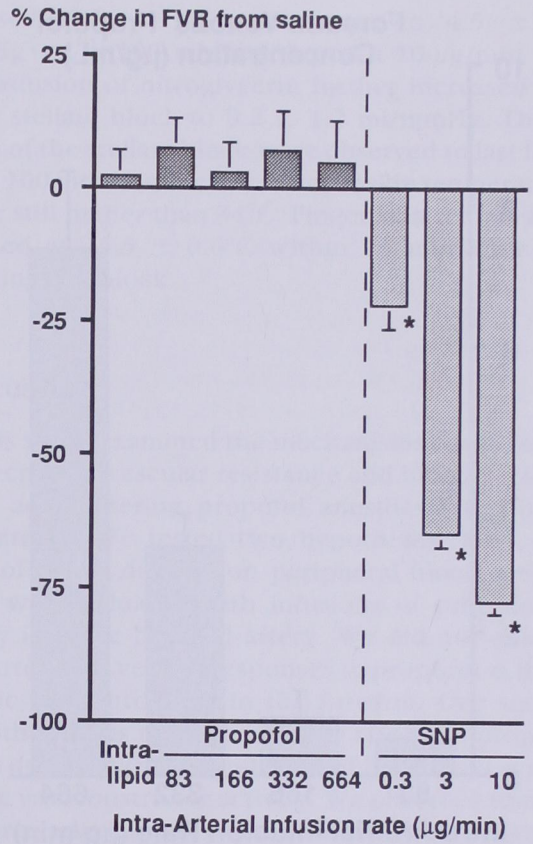

Fig. 1. Change in forearm vascular resistance (FVR) during brachial artery infusions of intralipid, propofol, and sodium nitroprusside (SNP). Intraarterial infusions of propofol did not change FVR, whereas intraarterial infusions of SNP significantly reduced FVR. Data are expressed as the percentage change from saline and are shown as mean ± SEM. *$P < 0.05$ indicates significant change from saline.

Study 2: Propofol Anesthesia after Left Stellate Ganglion Blockade

The effects of stellate blockade and propofol anesthesia are summarized in table 2. Stellate ganglion blockade decreased FVR by 14 ± 2 mmHg · ml^{-1} · 100 ml · min^{-1} ($P < 0.0001$) and increased FVC by 2.1 ± 0.3 ml/mmHg ($P < 0.0001$). Skin blood flow as assessed by the ratio of stellate to control photoplethysmographic wave amplitudes nearly doubled after stellate blockade ($P < 0.05$). Left stellate ganglion blockade significantly increased right (control) arm FVR by 5 mmHg · ml^{-1} · 100 ml · min^{-1} ($P < 0.005$). General anesthesia with propofol at 125 and 200 μg · kg^{-1} · min^{-1} reduced mean arterial pressure from 85 ± 3 mmHg to 69 ± 5 and 66 ± 4 mmHg, respectively ($P < 0.01$). Arterial plasma propofol concentrations were measured at 5 ± 0.7 μg/

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/86/1/64/365081/0000542-199701000-00010.pdf by guest on 10 April 2024

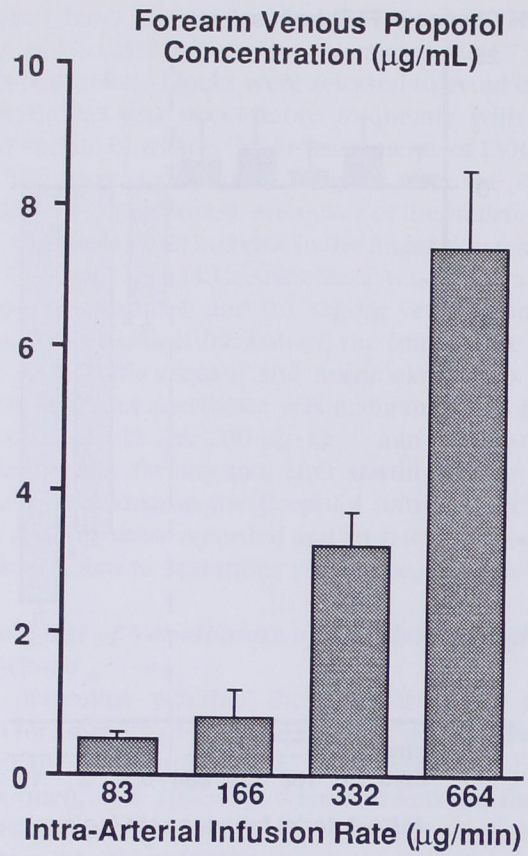

Fig. 2. Venous plasma propofol concentrations measured from the forearm during brachial artery infusions. Data are shown as mean ± SEM.

ml and 6.9 ± 0.6 μg/ml during systemic propofol infusions at 125 and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. Heart rate was unchanged (from 64 ± 6 bpm to 62 ± 4 and 63 ± 4 bpm, respectively). In the stellate ganglion blockade arm, FVR and FVC were not significantly different from preinduction (poststellate) values during propofol anesthesia. In the control (unblocked) arm during the 125 and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol infusions, FVR significantly decreased by 16.4 ± 5.4 $mmHg \cdot ml^{-1} \cdot 100\ ml \cdot min^{-1}$ and 17.5 ± 6 $mmHg \cdot ml^{-1} \cdot 100\ ml \cdot min^{-1}$, respectively ($P < 0.005$), and FVC significantly increased by 2.4 ± 1.2 ml/mmHg and 1.5 ± 0.6 ml/mmHg, respectively ($P < 0.05$). Skin blood flow ratios did not change during propofol anesthesia. The changes, expressed as percentages of baseline, in FVR and FVC after stellate ganglion blockade and during propofol anesthesia are shown in figure 3. The percentage of FVR changes from baseline were significantly different between blocked and unblocked arms during both rates of propofol infusion; FVR decreased by 59 ± 7% and 60 ± 6% in the arm with sympathetic denervation, whereas in the control arm the decrease was 37 ± 9% and 38 ± 10%, respectively ($P < 0.04$). The increases in FVC during propofol anesthesia were not different in the control and sympathetic denervation arms.

The Effect of Vasodilators and Stellate Ganglion Blockade

Before the stellate blockade, FVR decreased in all participants from a baseline of 24.2 ± 6.4 $mmHg \cdot ml^{-1} \cdot 100\ ml \cdot min^{-1}$ to 7.8 ± 1.5 $mmHg \cdot ml^{-1} \cdot 100\ ml \cdot min^{-1}$ during a 10-μg/min infusion of SNP, and FVC increased from a baseline of 5.9 ± 0.2 ml/mmHg to 7.6 ± 0.9 ml/mmHg during a 10-μg/min infusion of nitroglycerin. The sympathectomy resulting from the stellate ganglion block-

Table 2. Changes from Baseline in Forearm Vascular Resistance (FVR), Forearm Venous Compliance (FVC), and Skin Blood Flow (SBF) in Stellate Blockade Arm and Control Arm

	Baseline	Poststellate Blockade (change from baseline)	Propofol Infusion Rate	
			125 $\mu g \cdot kg \cdot min^{-1}$	200 $\mu g \cdot kg \cdot min^{-1}$
FVR ($mmHg \cdot ml^{-1} \cdot 100\ ml \cdot min$)				
Stellate blockade arm	28 ± 3	−14 ± 2*	−17 ± 3*	−17 ± 3*
Control arm	46 ± 5	5 ± 3*	−16 ± 5*,†	−18 ± 6*,†
FVC ($ml \cdot mmHg^{-1}$)				
Stellate blockade arm	3.9 ± 0.8	2.1 ± 0.3*	1.6 ± 0.3*	1.3 ± 0.3*
Control arm	2.7 ± 0.2	−0.3 ± 0.4	2.4 ± 1.2*,†	1.5 ± 0.6*,†
SBF, stellate blockade arm:control arm ratio	0.97 ± 0.11	0.88 ± 0.47*	−0.08 ± 0.18	−0.15 ± 0.17

Data are shown following stellate blockade but prior to induction of anesthesia, and following induction of anesthesia, at two infusion rates of anesthesia.
* $P < 0.05$, significant change from baseline, ANOVA.
† $P < 0.05$, significant change from poststellate, ANOVA.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/86/1/64/365081/0000542-199701000-00010.pdf by guest on 10 April 2024

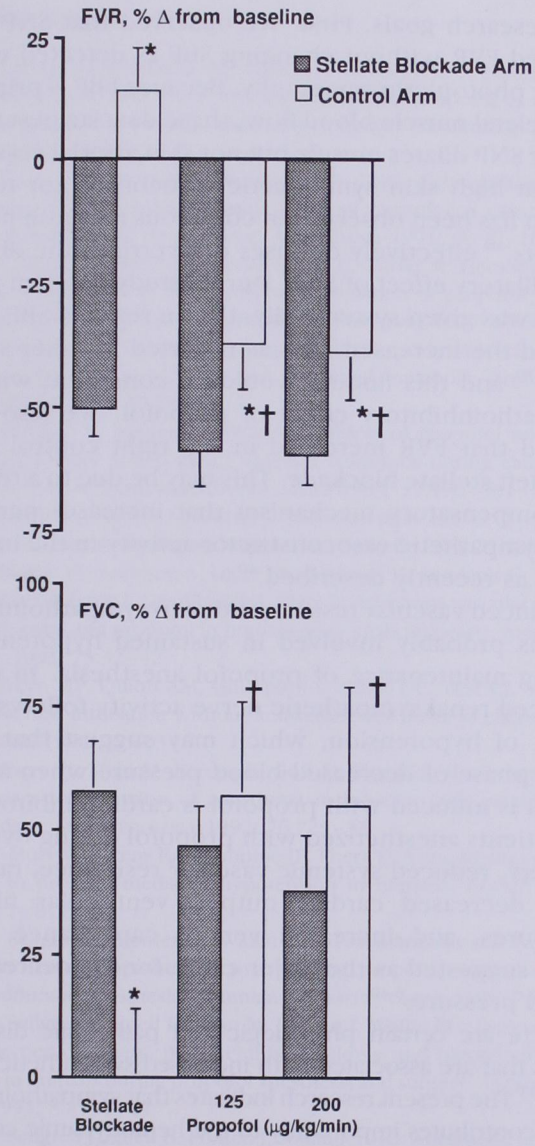

Fig. 3. Percentage changes from awake baseline in forearm vascular resistance (FVR) and forearm venous compliance (FVC) in the left arm after stellate blockade and in the control unblocked arm before and during propofol anesthesia. Stellate blockade decreased FVR and increased FVC on the side of the blockade. During propofol anesthesia, there was no further arterial or venous dilation in the sympathectomized arm, but significant dilation occurred in the unblocked control arm. Data are mean ± SEM. *$P < 0.05$ indicates significant difference between arms. †$P < 0.05$ indicates significant change from prepropofol baseline.

ade decreased resting FVR to 12.1 ± 2.6 $mmHg \cdot ml^{-1} \cdot 100\ ml \cdot min^{-1}$ and increased resting FVC to 7.4 ± 0.2 ml/mmHg. Arterial infusion of SNP (10 μg/min) after the stellate blockade further decreased FVR in all participants to 4.5 ± 0.1 $mmHg \cdot ml^{-1} \cdot 100\ ml \cdot min^{-1}$, and a 10-μg/min arterial infusion of nitroglycerin further increased FVC after stellate block to 9.2 ± 1.2 ml/mmHg. The effects of the stellate block were observed to last for at least 100 min, at which time finger skin temperatures were still higher than 34°C. Finger skin temperature peaked at 34.5 ± 0.6°C within 15 min after performing the block.

Discussion

This study examined the mechanisms contributing to decreased vascular resistance and blood pressure after administering propofol anesthesia to human volunteers. We tested two hypotheses. First, that propofol acts directly on peripheral blood vessels. This was evaluated with infusions of propofol directly into the brachial artery. We did not observe any arterial or venous responses to propofol at therapeutic concentrations in the forearm. Our second hypothesis was that the vascular effects of propofol were due, in part, to inhibition of peripheral sympathetic vasoconstrictor activity. We observed that the forearm arterial and venous vasodilation responses to intravenous propofol anesthesia were similar to the effects of stellate ganglion blockade. In addition, there was no further enhancement of vasodilation within the sympathetically blocked forearm during propofol anesthesia, although we showed that increased vasodilatation is possible in the sympathetically denervated arm in response to the vasodilators, SNP, and nitroglycerin. Thus the mechanism of propofol-mediated arterial and vein dilation is more likely due to an inhibition of tonic sympathetic vasoconstrictor outflow[9,11-13] than to direct vascular relaxation.

Animal investigations using *in vitro* methods have suggested that propofol acts directly to relax smooth muscle and that propofol is a more potent dilator of veins than arteries.[14,19] Other studies have suggested that these effects are mediated by the actions of propofol on the endothelium, which stimulates nitric oxide release,[14,20,21] or by the modulation of endogenous norepinephrine release and neuroeffector coupling.[30] Several explanations are possible for the inconsistency of our findings and those of the reported *in vitro* preparations. The vascular effects of propofol have been shown *in vitro* only when tissue perfusion propofol concentra-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/86/1/64/365081/0000542-199701000-00010.pdf by guest on 10 April 2024

tions exceed therapeutic concentrations.[14-19] Furthermore, *in vitro* studies that have reported vasodilation with propofol at perfusate concentrations similar to therapeutic concentrations (*e.g.*, 10^{-5} M) have not compensated for the usual protein binding of propofol. The clinically relevant plasma concentrations of propofol range from 2-10 μg/ml (*i.e.*, approximately $1-5 \times 10^{-5}$ M), of which approximately 97-99% of propofol is protein bound.[31] Other limitations of published *in vitro* studies that may explain the disparity between results include the use of vascular rings from large conducting arteries that might not reflect the actions of propofol on the smaller arterioles and precapillary sphincters that control vascular resistance, and the unclear issue of species differences.

The use of brachial artery infusions obviates many problems with *in vitro* studies. In the brachial artery infusion study, we measured the response in humans and assayed plasma propofol in the forearm vein to verify that therapeutic concentrations were achieved in the forearm and in the presence of usual propofol-plasma protein binding. Although we are unaware of any reports of deliberate administration of propofol into human arteries, our dose-escalating, pilot studies revealed no untoward effect of intraarterial infusions. Accidental intraarterial injections of large concentrations of propofol have been reported in several cases and, apart from complaints of severe pain on injection and transient decreases in blood flow, no significant or permanent complications occurred.[32-35] None of our participants reported discomfort during the propofol infusions, and no adverse sequelae occurred, which probably reflects the small infusion concentrations and the likelihood that endothelial injury in arteries exposed to propofol did not occur.[36]

Induction of anesthesia with propofol has been associated with a decreased mean arterial pressure associated with marked reductions of efferent muscle sympathetic nerve activity and plasma catecholamines.[9,11-13] This reduction of sympathetic nerve activity is a result of decreases in both the tonic level of sympathetic activity and the baroreflex control of sympathetic nerve activity.[9,12] The present study indicates that the reduction of peripheral sympathetic vasoconstrictor activity is an important mechanism for the vasodilation associated with propofol anesthesia. Sympathetic inhibition leads to both arterial and venous dilation that can reduce systemic vascular resistance and venous return to the heart.[37]

We note several findings that were not central to our research goals. First, we observed that SNP decreased FVR without changing SBF as detected with finger photoplethysmography. Because FBF is primarily skeletal muscle blood flow, these data suggest that either SNP dilates muscle but not skin arterial vessels, or that high skin sympathetic vasoconstrictor tone, which has been observed in conscious research participants,[38] effectively opposes or overrides the direct vasodilatory effect of SNP. During study 2, when propofol was given systemically, the increase in SBF paralleled the increased FBF, as reported in other studies,[11,39] and this finding would be consistent with a sympathoinhibitory effect of propofol. We also observed that FVR increased in the right control arm after left stellate blockade. This may be due to a reflex or compensatory mechanism that increases peripheral sympathetic vasoconstrictor activity in the intact limb, as recently described.[40]

Reduced vascular resistance due to sympathoinhibition is probably involved in sustained hypotension during maintenance of propofol anesthesia. In rats, reduced renal sympathetic nerve activity follows the onset of hypotension, which may suggest that the early phase of decreased blood pressure when anesthesia is induced with propofol is cardioinhibitory.[41] In patients anesthetized with propofol during bypass surgery, reduced systemic vascular resistance, rather than decreased cardiac output, ventricular filling pressures, and increased venous capacitance, has been suggested as the major cause for the decreased blood pressure.[6,42]

There are certain physiologic and pathologic disease states that are associated with increased sympathetic outflow.[43] The present research indicates that sympathoinhibition contributes importantly to the hemodynamic consequences of propofol anesthesia. In the face of increased sympathetic outflow, it is conceivable that the sympathoinhibitory effects of propofol might result in exaggerated hemodynamic consequences. Thus elderly patients, patients with cardiac disease, and those who are anxious might be prone to greater decreases in blood pressure with propofol. This is particularly important because, in contrast to *in vitro* studies in animals, our data indicate that propofol did not have direct effects on arterial or venous vascular smooth muscle.

The authors thank Jill Barney, Linda Messana, and Toni Uhrich for help in conducting these studies, data reduction, graphical and statistical data analyses, and in preparing and refining the manuscript. They thank Deborah Raybuck of Zeneca Pharmaceuticals for providing the plasma propofol determinations.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/86/1/64/365081/0000542-199701000-00010.pdf by guest on 10 April 2024

References

1. Lepage J-YM, Pinaud ML, Helias JH, Cozian AY, Le Normand Y, Souron RJ: Left ventricular performance during propofol or methohexital anesthesia: Isotopic and invasive cardiac monitoring. Anesth Analg 1991; 73:3–9

2. Gauss A, Heinrich H, Wilder-Smith OHG: Echocardiographic assessment of the haemodynamic effect of propofol: A comparison with etomidate and thiopentone. Anaesthesia 1991; 46:99–105

3. Coates DP, Monk CR, Prys-Roberts C, Turtle M: Hemodynamic effects of infusions of the emulsion formulation of propofol during nitrous oxide anesthesia in humans. Anesth Analg 1987; 66:64–70

4. Laycock GJA, Alston RP: Propofol and hypothermic cardiopulmonary bypass. Vasodilation and enhanced metabolic protection? Anaesthesia 1992; 47:382–7

5. Pensado A, Molins N, Alvarez J: Effects of propofol on mean arterial pressure and systemic vascular resistance during cardiopulmonary bypass. Acta Anaesthesiol Scand 1993; 37:498–501

6. Pensado A, Molins N, Alvarez J: Haemodynamic effects of propofol during coronary artery bypass surgery. Br J Anaesth 1993; 71:586–8

7. Rouby J-J, Andreev A, Leger Ph, Arthaud M, Landault C, Vicaut E, Maistre G, Eurin J, Gandjbakch I, Viars P: Peripheral vascular effects of thiopental and propofol in humans with artificial hearts. ANESTHESIOLOGY 1991; 75:32–42

8. Steyn MP, Quinn AM, Gillespie JA, Miller DC, Best CJ, Morton NS: Tracheal intubation without neuromuscular block in children. Br J Anaesth 1994; 72:403–6

9. Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP: Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. ANESTHESIOLOGY 1992; 76:725–33

10. Muzi M, Berens RA, Kampine JP, Ebert TJ: Venodilation contributes to propofol-mediated hypotension in humans. Anesth Analg 1992; 74:877–83

11. Sellgren J, Ponten J, Wallin BG: Percutaneous recording of muscle nerve sympathetic activity during propofol, nitrous oxide, and isoflurane anesthesia in humans. ANESTHESIOLOGY 1990; 73:20–7

12. Sellgren J, Ejnell H, Elam M, Ponten J, Wallin BG: Sympathetic muscle nerve activity, peripheral blood flows, and baroreceptor reflexes in humans during propofol anesthesia and surgery. ANESTHESIOLOGY 1994; 80:534–44

13. Sellgren J, Ejnell H, Ponten J, Sonander HG: Anesthetic modulation of the cardiovascular response to microlaryngoscopy. A comparison and propofol and methohexital with special reference to leg blood flow, catecholamines and recovery. Acta Anaesthesiol Scand 1995; 39:381–9

14. Bentley GN, Gent JP, Goodchild CS: Vascular effects of propofol: Smooth muscle relaxation in isolated veins and arteries. J Pharm Pharmacol 1989; 41:797–8

15. Nakamura K, Hatano Y, Hirakata H, Nishiwada M, Toda H: Direct vasoconstrictor and vasodilator effects of propofol in isolated dog arteries. Br J Anaesth 1992; 68:193–7

16. Petros AJ, Bogle RG, Pearson JD: Propofol stimulates nitric oxide release from cultured porcine aortic endothelial cells. Br J Pharmacol 1993; 109:6–7

17. MacPherson RD, Rasiah RL, McLeod LJ: Propofol attenuates the myogenic response of vascular smooth muscle. Anesth Analg 1993; 76:822–9

18. Mimaroglu C, Utkan T, Kaya T, Kafali H, Sarioglu Y: Effects of propofol on vascular smooth muscle function in isolated rat aorta. Meth Find Exp Clin Pharmacol 1994; 16:257–61

19. Kamitani K, Yamazaki M, Yukitaka M, Ito Y, Momose Y: Effects of propofol on isolated rabbit mesenteric arteries and veins. Br J Anaesth 1995; 75:457–61

20. Miyawaki I, Nakamura K, Terasako K, Toda H, Kakuyama M, Mori K: Modification of endothelium-dependent relaxation by propofol, ketamine, and midazolam. Anesth Analg 1995; 81:474–9

21. Park KW, Dai HB, Lowenstein E, Sellke FW: Propofol-associated dilation of rat distal coronary arteries is mediated by multiple substances, including endothelium-derived nitric oxide. Anesth Analg 1995; 81:1191–6

22. Shafer A, Doze VA, Shafer SL, White PF: Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. ANESTHESIOLOGY 1988; 69:348–56

23. Shafer L: Advances in propofol pharmacokinetics and pharmacodynamics. J Clin Anesth 1993; 5:14S–21S

24. Creager MA, Cooke JP, Mendelsohn ME, Gallagher SJ, Coleman SM, Loscalzo J, Dzau VJ: Impaired vasodilation of forearm resistance vessels in hypercholesterolemic humans. J Clin Invest 1990; 86:228–34

25. Rogers MC, Battit G, McPeek B, Todd D: Lateralization of sympathetic control of the human sinus node: ECG changes of stellate ganglion block. ANESTHESIOLOGY 1978; 48:139–41

26. Rogers MC, Abildskov JA, Preston JB: Cardiac effects of stimulation and block of the stellate ganglion. ANESTHESIOLOGY 1973; 39:525–33

27. Benjamin N, Calver A, Collier J, Robinson B, Vallance P, Webb D: Measuring forearm blood flow and interpreting the responses to drugs and mediators. Hypertension 1995; 25:918–23

28. Groban L, Cowley AW Jr, Ebert TJ: Atrial natriuretic peptide augments forearm capillary filtration in humans. Am J Physiol 1990; 259:H258–63

29. deTrafford J, Lafferty K: What does photoplethysmography measure? Med Biol Eng Comput 1984; 22:479–80

30. Biddle NL, Gelb AW, Hamilton JT: Propofol differentially attenuates the responses to exogenous and endogenous norepinephrine in the isolated rat femoral artery in vitro. Anesth Analg 1995; 80:793–9

31. Kirkpatrick T, Cockshott D, Douglas EJ, Nimmo WS: Pharmacokinetics of propofol (diprivan) in elderly patients. Br J Anaesth 1988; 60:146–50

32. Chong M, Davis TP: Accidental intra-arterial injection of propofol. Anaesthesia 1987; 42:781

33. Riley RH, Lincoln CA: Intra-arterial injection of propofol. Anaesth Intensive Care 1990; 18:269–70

34. Holley HS, Cuthrell L: Intraarterial injection of propofol. ANESTHESIOLOGY 1990; 73:183–4

35. Brimacombe J, Gandini D, Bashford L: Transient decrease in arm blood flow following accidental intra-arterial injection of propofol into the left brachial artery. Anaesth Intensive Care 1994; 22:291–2

36. MacPherson RD, Rasiah RL, McLeod LJ: Intraarterial propofol is not directly toxic to vascular endothelium. ANESTHESIOLOGY 1992; 76:967–71

37. Smith JJ, Kampine JP: Circulatory Physiology—The Essentials. Baltimore, Williams & Wilkins, 1984, pp 1–317

38. Bini G, Hagbarth K-E, Hynninen P, Wallin BG: Thermoregulatory and rhythm-generating mechanisms governing the sudomotor and vasoconstrictor outflow in human cutaneous nerves. J Physiol 1980; 306:537–52

39. Robinson BJ, Buyck HCE, Galletly DC: Effect of propofol on

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/86/1/64/365081/0000542-199701000-00010.pdf by guest on 10 April 2024

heart rate, arterial pressure and digital plethysmograph variability. Br J Anaesth 1994; 73:167–73

40. Ikeda T, Iwase S, Sugiyama Y, Matsukawa T, Mano T, Doi M, Kikura M, Ikeda K: Stellate ganglion block is associated with increased tibial nerve muscle sympathetic activity in humans. ANESTHESIOLOGY 1996; 84:843–50

41. Krassioukov AV, Gelb AW, Weaver LC: Action of propofol on central sympathetic mechanisms controlling blood pressure. Can J Anaesth 1993; 40:761–9

42. Baraka A, Dabbous A, Siddik S, Bijjani A: Action of propofol on resistance and capacitance vessels during cardiopulmonary bypass. Acta Anaesthesiol Scand 1991; 35:545–7

43. Johnson RH, Spalding JMK: Disorders of the autonomic nervous system. Philadelphia, FA Davis, 1974, pp 1–284

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/86/1/64/365081/0000542-199701000-00010.pdf by guest on 10 April 2024