Anesthesiology
77:956–963, 1992

Effects of Propofol and Thiopental in Isolated Rat Aorta and Pulmonary Artery

Wyun Kon Park, M.D., Carl Lynch III, M.D., Ph.D.,† Roger A. Johns, M.D.†*

This study was performed to determine if direct arterial dilating actions of propofol contribute to the drug's hypotensive actions. The effects of propofol were compared with those of thiopental on isolated vascular ring preparations from rat thoracic aorta and pulmonary artery. Thoracic aortic ring responses were evaluated in the presence and absence of endothelium, indomethacin, and N$^{\omega}$-nitro-L-arginine methyl ester (LNAME; a specific inhibitor of endothelium-derived relaxing factor–nitric oxide [EDRF/NO] synthase). Pulmonary artery responses were investigated with intact endothelium. After the induction of active isometric force by a predetermined EC_{50} dose of phenylephrine for each ring, effects of propofol (30, 100, 300 μM) and thiopental (10, 30, 100 μM) were examined. Propofol caused significant vasodilation in endothelium-intact, endothelium-denuded, and LNAME-treated aortic rings. In the endothelium-intact aortic and pulmonary artery rings, the initial vasodilation due to 30 and 100 μM propofol showed gradual and partial recovery over 15 min; 300 μM propofol caused sustained vasodilation. Endothelium-denuded rings and LNAME-pretreated endothelium-intact rings showed constant and sustained vasodilation with all propofol concentrations. Propofol also caused marked vasodilation in pulmonary arteries. In contrast, thiopental had no vasodilating effect in aortic or pulmonary artery preparations. In control experiments, propofol vehicle (Intralipid®) also had no effect on vascular rings. Indomethacin pretreatment induced a dose-dependent vasoconstriction by thiopental in endothelium-intact rings and decreased the vasodilation due to propofol. These results suggest that propofol directly relaxes arterial smooth muscle, with subsequent progressive attenuation, possibly through the gradual inhibition of EDRF/NO production. Effects in the presence of indomethacin suggest that propofol and thiopental induce the release of vasodilating cyclooxygenase metabolites from vascular rings with intact endothelium. (Key words: Anesthetics, intravenous: propofol; thiopental. Animals: rats. Arteries: aorta; pulmonary arteries. Endothelium: endothelium-derived relaxing factor. Pharmacology: indomethacin; N$^{\omega}$-nitro-L-arginine methyl ester; phenylephrine.)

IN CLINICAL ANESTHESIA, propofol (2,6-diisopropylphenol) has appeared to be a useful alternative to thiopental as an induction agent because of its rapid onset, short duration of action, and rapid elimination.[1] Previous studies on the cardiovascular effects of propofol at clinically relevant doses have reported that relatively marked hypotension occurs after its administration.[2] However, clinical studies on the hemodynamic effects of propofol have provided conflicting evidence with regard to its relative effects on cardiac output and systemic vascular resistance. Several investigations reported that the decrease in arterial pressure after administration of propofol is caused by a decrease in systemic vascular resistance with little or no change in preload and cardiac output.[2–4] Others have suggested that the reduction in arterial pressure after propofol is related primarily to a significant decrease in cardiac output or stroke volume without concomitant changes in systemic vascular resistance.[5,6] Furthermore, in studies in swine, Coetzee *et al.*[7] found that increasing propofol plasma concentration was related to a decrease in myocardial contractility and to a dose-dependent increase in peripheral vascular resistance. Although studies suggest that reduction in both cardiac output and systemic vascular resistance are responsible for the decrease in systemic arterial pressure,[8,9] the mechanism by which vasodilation contributes to the hypotension seen with propofol is unclear. In view of these conflicting results of propofol on systemic vascular resistance, we measured the direct effect of propofol in rat thoracic aorta and pulmonary artery and compared these effects to those produced by thiopental. The potential interaction with endothelium-derived relaxing factor (EDRF) also was explored using endothelium-denuded rings or rings in which EDRF/nitric oxide (NO) synthase was inhibited.

Materials and Methods

According to a protocol approved by the University of Virginia Animal Research Committee, male Sprague-Dawley rats (300–350 g) were killed by decapitation under methoxyflurane anesthesia. The thoracic aorta and heart and lung were dissected and removed *en bloc* and immediately placed in Krebs solution (millimolar: NaCl 111, KCl 5.0, NaH_2PO_4 1.0, $MgCl_2$ 1.2, $NaHCO_3$ 25, $CaCl_2$ 2.0, glucose 11.1) bubbled with 95% O_2/5% CO_2, with *p*H maintained at 7.45 ± 0.5. Adhering fat and connective tissues were gently dissected from the aorta and first-branch pulmonary arteries. The vessels then were sliced into 2–3-mm ring segments under microscopic observation, typically yielding six aortic and two pulmonary artery rings. In designated experiments the endothelium of aortic rings was mechanically removed by turning a ring gently five or six times on the distal portion of a small forceps. The aortic and pulmonary artery rings were suspended on triangular-shaped stainless steel hooks with 20 mN of applied resting force (that exerted by gravity on

* Visiting Research Assistant Professor.

† Associate Professor of Anesthesiology.

Received from the Department of Anesthesiology, University of Virginia Health Sciences Center, Charlottesville, Virginia. Accepted for publication July 14, 1992.

Address reprint requests to Dr. Johns: Department of Anesthesiology, Box 238, University of Virginia Health Sciences Center, Charlottesville, Virginia 22908.

2 g mass) in 10-ml water-jacketed tissue baths containing Krebs solution gassed with 95% O_2/5% CO_2. Bath temperature and *p*H were maintained at 37° C and 7.45 ± 0.5, respectively. The force was measured isometrically using a Grass FT03 force displacement transducer and continuously displayed on a Gould 2800 recorder. The Krebs solution was changed every 15 min during a 90-min equilibration period during which the resting force was maintained and periodically adjusted to 20 mN.

The functional integrity of the endothelium was determined by the addition of methacholine (1×10^{-6} M), and rings exhibiting relaxation of less than 30% were discarded. In aortic rings from which the endothelium had been removed, the absence of endothelium was confirmed by no response or by slight vasoconstriction after administration of methacholine (1×10^{-6} M). The rings were then washed several times with Krebs solution until they returned to resting force.

Experimental Protocols

The aortic ring experiments were divided into the following groups: endothelium-intact and -denuded rings, N^{ω}-nitro-L-arginine methyl ester (LNAME; a specific inhibitor of EDRF/NO synthase)[10]–pretreated endothelium-intact rings, and indomethacin-pretreated endothelium-intact and -denuded rings. The concentration of phenylephrine required to generate half-maximal force (EC_{50}) was determined by incremental administration of 10^{-10} to 10^{-6} M phenylephrine in each ring studied. Denuded and LNAME-treated rings showed no differences in dose response, and each generated significantly greater force than endothelium-intact rings in response to phenylephrine concentrations ≥ 5 nM (fig. 1). This greater phenylephrine sensitivity is consistent with the elimination of basal and phenylephrine-stimulated EDRF release by removal of the endothelium[11] or inhibition of EDRF/NO synthase.

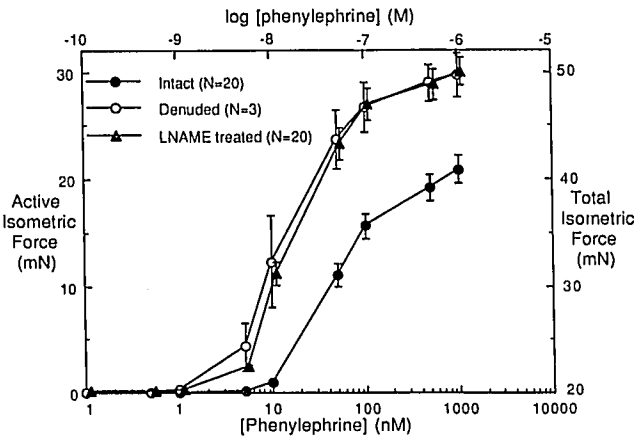

FIG. 1. Phenylephrine concentration response curve among endothelium-intact, endothelium-denuded, and LNAME-treated endothelium-intact aortic rings. Results are expressed as mean ± SEM for n experiments.

After washing and relaxation, a stable contraction in response to the phenylephrine EC_{50} was obtained. Thiopental was added from a 56 mM stock solution to the baths in a cumulative manner to obtain 10, 30, and 100 μM, with 15 min between additions. Propofol was applied in its commercially available 10% Intralipid® emulsion (56 mM or 10 mg/ml propofol, 10% soybean oil, 2.25% glycerol, 1.2% purified phospholipid) cumulatively to obtain 30, 100, and 300 μM. Because of the presence of lipid in solution and the 5,000:1 lipid:aqueous partitioning,‡ calculated aqueous phase concentrations were 22, 46 and 66 μM. In a separate series of control experiments, volumes of 10% Intralipid® identical to those used to yield each concentration of propofol were used. Each ring was then washed several times with Krebs solution to obtain the baseline force, contracted again with the predetermined EC_{50} dose of phenylephrine, and relaxed with methacholine (1×10^{-6} M) to confirm the functional integrity of the endothelium.

To define the role of EDRF, 300 μM LNAME was added to the bath 20 min before the determination of the phenylephrine EC_{50} and was maintained in the bath throughout the duration of the experiments. In experiments designed to prevent conflicting effects of cyclooxygenase-derived arachidonic acid metabolites, indomethacin (2.8×10^{-6} M) was added to the bath 20 min before the determination of the EC_{50} concentration of phenylephrine and was maintained throughout the experimental period. To provide comparison with responses in aortic rings, the vascular effects of increasing concentrations of propofol, Intralipid, and thiopental were investigated only in endothelium-intact pulmonary artery rings.

Pharmacologic Agents

Phenylephrine, methacholine, indomethacin, and LNAME were obtained from Sigma Chemical Co. (St. Louis, MO). These drugs were prepared in Krebs solution, with the exception of indomethacin, which was dissolved in a 150 mM $NaHCO_3$ solution (*p*H 8.8), and adjusted to a *p*H of 7.4 with 2 N HCl. Thiopental was obtained from Abbot Laboratories (Chicago, IL), Intralipid® from KabiVitrum Inc. (Alameda, LA), and propofol from Stuart Pharmaceuticals (Wilmington, DE).

Statistical Analysis

To test for significant changes, the absolute values of force due to the EC_{50} phenylephrine concentration and

‡ ICI Pharmaceuticals: Personal communication.

values after drug applications were compared by repeated-measures analysis of variance followed by Scheffé's multiple comparison test. For clarity, results are presented as percent change from control force. Comparison (as percent change from control) between endothelium-intact *versus* endothelium-denuded groups was made using the two-tailed Student's unpaired t test. All values are expressed as mean ± SEM; $P < 0.05$ was considered significant.

Results

Aortic Vessels

Vascular Effects in Indomethacin-untreated Vessels

Effects of Intralipid, propofol, and thiopental on aortic ring force are shown in figure 2. When administered in concentrations equivalent to that of 30, 100, and 300 μM propofol, the Intralipid® emulsion had no vascular effect on either endothelium-intact or -denuded aortic preparations. In contrast, propofol at 30, 100, and 300 μM significantly relaxed endothelium-intact aortic rings compared to both thiopental and control. While propofol vasorelaxation in endothelium-intact rings did not differ between successive doses, significant dose-dependence ($P < 0.05$, analysis of variance) of vasodilation was seen in endothelium-denuded rings (fig. 2B). Thiopental at 10, 30, and 100 μM, as well as Intralipid, produced virtually no effects on aortic rings, and there were no significant differences in their vascular actions between endothelium-intact and -denuded preparations.

It is noteworthy, however, that in the endothelium-intact aortic rings, 30 and 100 μM propofol caused maximum arterial dilation after approximately 4–8 min, followed by partial and gradual recovery of force. In figure 3, the difference between the intact and denuded vessels is depicted in the force tracings from two rings. The vascular tissue with intact endothelium shows clear evidence of partial recovery of force after 5–8 min, a phenomenon not observed in the denuded ring. Figure 4 plots the maximal decrease in force and that observed at the end of the exposure to each propofol concentration. In intact vessels, the relaxation at the end of the 15-min exposure to 30 μM propofol was only 51% of maximal (at 6–9 min); relaxation was 73% of maximal at the end of the period in 100 μM propofol. In 300 μM propofol, both endothelium-denuded and -intact rings had maintained relaxation, with no evidence of reversal. The LNAME-pretreated rings behaved in a manner similar to endothelium-denuded rings, demonstrating persistent vasodilation at propofol 30, 100, and 300 μM. Furthermore, LNAME-pretreated rings showed significantly greater vasodilation compared to endothelium-intact rings at the period of maximum vasodilation at 100 and 300 μM propofol (fig. 5).

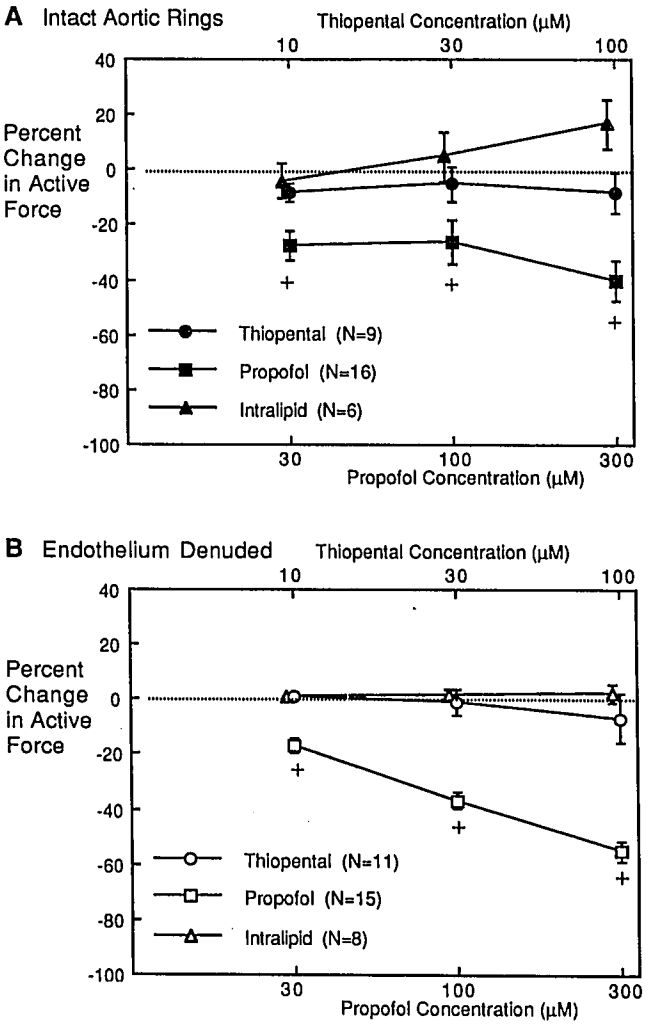

FIG. 2. Dose-dependent vasoactive effects of propofol, thiopental, or Intralipid vehicle on endothelium-intact (*A*) or endothelium-denuded (*B*) aortic rings. Results are plotted as the percent change from the force induced by an EC_{50} concentration of phenylephrine applied to each ring. The values represent maximal response after each dose of each drug and are expressed as mean ± SEM for n experiments. Intralipid was applied in concentrations (0.0054, 0.018, 0.054%) equivalent to those obtained when 30, 100, and 300 μM propofol was added in its Intralipid vehicle. + $P < 0.05$ for changes in absolute force by analysis of variance.

Vascular Effects in Indomethacin-treated Vessels

Indomethacin partially blunted the vasodilatory effect of propofol (table 1). In tissue with endothelium, the maximal vasodilating response of 30 μM propofol was significantly ($P < 0.05$) reduced by indomethacin pretreatment, and the final level of relaxation was reduced by 100 and 300 μM propofol. In denuded rings, the relaxant action of only 30 μM propofol was impaired. In contrast

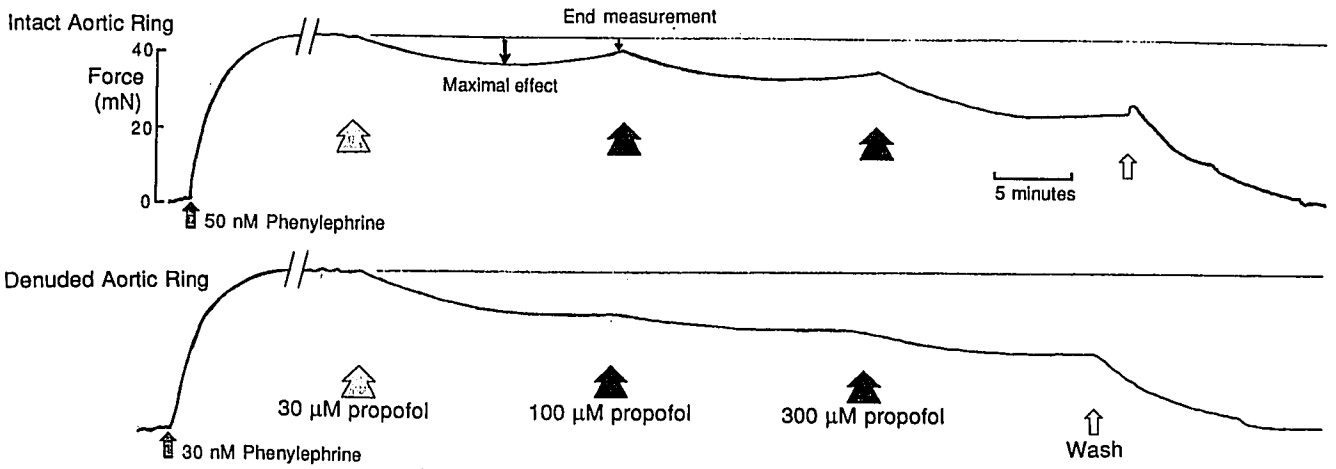

FIG. 3. Characteristic force tracings showing the response to application of propofol to either an endothelium-intact or an endothelium-denuded aortic ring, each constricted with the predetermined EC_{50} phenylephrine concentration for that ring. The relaxation caused by 30 and 100 μM propofol shows partial reversal in the endothelium-intact ring.

to results in its absence, in the presence of indomethacin in endothelium-intact rings thiopental caused a significant dose-dependent enhancement of vasoconstriction at all doses. However, indomethacin had no effect on thiopental responses in denuded rings (fig. 6).

PULMONARY VESSELS

Administration of 100 μM thiopental caused a modest but significant vasoconstriction (23 ± 9%, $P < 0.05$). Propofol 30, 100, and 300 μM significantly vasodilated the pulmonary artery preparations, although the effects did not differ significantly between successive doses (fig. 7). Propofol 100 μM showed maximal arterial dilation and gradual recovery over the same period of administration as with the intact aortic rings. Although 30 μM propofol showed the same vasodilating pattern as did 100 μM propofol, the difference between maximal vasodilation and partial recovery at 15 min after administration was not statistically significant ($P = 0.08$, paired t test). Thirty percent recovery was observed with 100 μM propofol, but at 300 μM, relaxation was sustained during the administration. As with the aortic rings, Intralipid® alone caused no alteration in response of the pulmonary vessels.

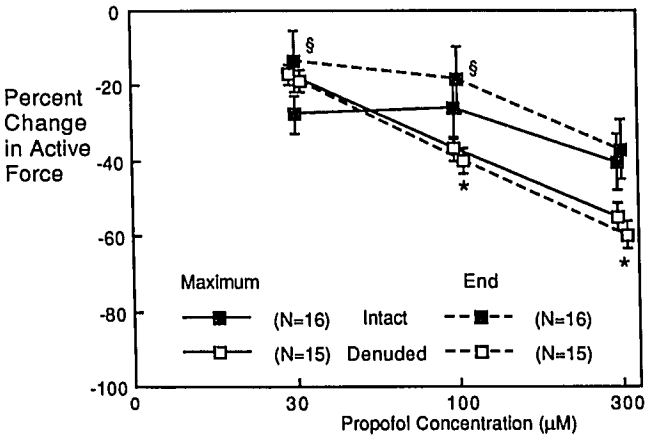

FIG. 4. The effects of increasing concentrations of propofol in endothelium-intact and endothelium-denuded aortic rings on the initial maximum vasodilation (*solid lines*) and at the end of 15 min propofol administration (*dashed lines*). Values are expressed as mean ± SEM for n experiments. §$P < 0.05$ for difference between maximal and end change in force at each propofol concentration by paired t test. *$P < 0.05$ for difference in force between endothelium-intact and endothelium-denuded rings at the end of the propofol administration period.

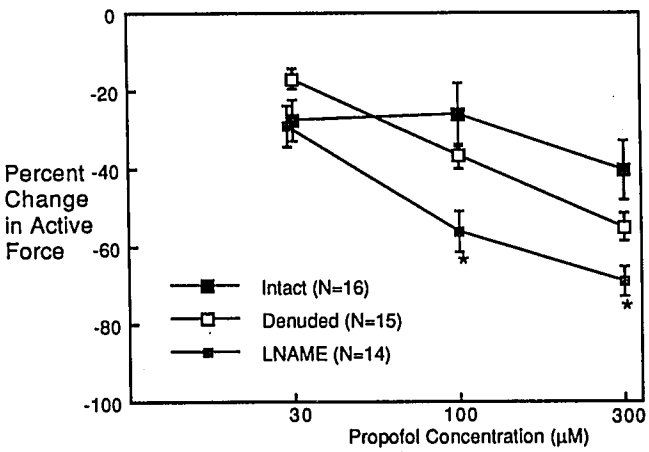

FIG. 5. The effects of increasing concentrations of propofol on vascular relaxation in endothelium-intact, endothelium-denuded, and LNAME-treated endothelium-intact aortic rings at the period of maximum vasodilation. Results are plotted as the percent change (mean ± SEM for n experiments) from the constriction to EC_{50} phenylephrine concentration. *$P < 0.05$ for difference in force between endothelium-intact and LNAME-treated rings by unpaired t test.

TABLE 1. The Effects of Propofol on the Isometric Force in Endothelium-intact and Endothelium-denuded Thoracic Aortic Rings With or Without Indomethacin Pretreatment

Propofol Concentration (μM)		Endothelium-intact		Endothelium-denuded	
		With Indomethacin (n = 11)	Without Indomethacin (n = 16)	With Indomethacin (n = 8)	Without Indomethacin (n = 15)
30	Maximal	−7.0 ± 2.4*	−27.6 ± 5.1		
	Final	4.6 ± 4.9†	−13.5 ± 8.1†	−8.9 ± 1.6*	−18.8 ± 2.9
100	Maximal	−5.6 ± 5.3	−26.2 ± 8.1		
	Final	2.8 ± 7.2*†	−18.6 ± 9.0†	−25.4 ± 2.4	−40.0 ± 3.4
300	Maximal	−22.2 ± 8.2	−40.5 ± 7.4		
	Final	−14.9 ± 8.5*†	−37.1 ± 8.0	−53.9 ± 3.1	−59.8 ± 3.6

Values are expressed as percent change (mean ± SEM for n rings) in active force due to EC_{50} phenylephrine concentration; a negative sign denotes relaxation. Because of the partial reversal of relaxation in the endothelium-intact rings, the maximal vasodilation due to propofol is shown, as is the final change in force at the end of the observation period.

* $P < 0.05$ absence of *versus* pretreatment with indomethacin by two-tailed unpaired *t* test.

† $P < 0.05$ maximal *versus* final change in force at each propofol concentration by paired *t* test.

Discussion

Several clinical reports showed that reduction in systemic vascular resistance due to arterial vasodilation is at least partially responsible for the arterial hypotension observed after the clinical administration of propofol.[2–4,8,9] It is unclear from clinical data, however, whether the cause of the decrease in systemic vascular resistance is related to 1) a direct vasodilating effect; 2) a reduction of sympathetic outflow to the arterial system by deepening of anesthesia; 3) an alteration of baroreflex activity; or 4) a combination of these effects. Our results in isolated aortic rings clearly demonstrate that a direct arterial vasodilation occurs with propofol.

The typical peak serum values for propofol are approximately 8 μg/ml (44 μM), with infusions yielding values of about 4–5 μg/ml (22 μM).[12] However, free drug concentrations may be markedly reduced by substantial protein binding of 97–98% measured at equilibrium.[13] The lowest calculated free propofol concentration (~ 22 μM) used in this study, which caused a 28 ± 5% relaxation, perhaps could represent as much as 20 times the peak free concentrations in serum. The microkinetic behavior within the vascular space (drug transfer rate from liposome to aqueous phase, to protein-bound state, and to cellular constituents), however, has not been defined. Protein binding in this setting is unlikely to be instanta-

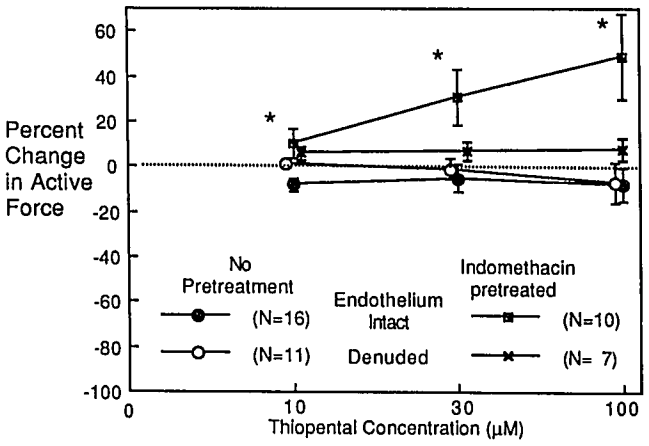

FIG. 6. Effects of indomethacin on dose-dependent thiopental-induced vascular actions in endothelium-intact and endothelium-denuded aortic rings. Results are plotted as the percent change from the constriction to an EC_{50} phenylephrine concentration. Values are expressed as mean ± SEM for n experiments. *$P < 0.05$ for differences in force between indomethacin- and non–indomethacin-treated endothelium-intact rings by unpaired *t* test.

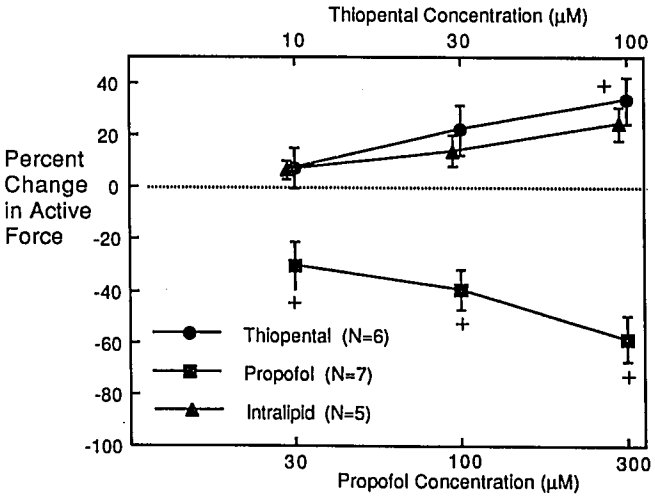

FIG. 7. Comparisons of the dose-dependent vascular actions of propofol, thiopental, and Intralipid vehicle in endothelium-intact pulmonary arterial rings. Results are plotted as the percent change from the EC_{50} phenylephrine concentration. The values (mean ± SEM for n experiments) represent maximal responses after each dose of each drug. +$P < 0.05$ for changes in force by analysis of variance.

neous, so free drug concentrations with a bolus induction dose remain undefined. Also unknown is the possible direct interaction of the endothelium and vascular tissue with drug-containing liposomes that initially contain ~ 500 μM propofol.

A direct arterial vasodilating effect of propofol has been previously suggested. Glen[14] reported that propofol produced dose-dependent reductions in pressure in an isolated perfused cat hind limb and attributed them in part to a decrease in peripheral vascular resistance consistent with arterial vasodilation. A dose-dependent relaxing effect of propofol on isolated arterial and venous rings in rats was shown by Bentley *et al.*[15]; however, the presence of and possible role of endothelium was not addressed. Likewise, propofol (≥ 10 μM) was shown to cause relaxation of endothelin-induced contractions of isolated distal canine coronary artery; in contrast, it enhanced contractions in proximal coronary artery at ~ 10 μM before causing relaxation at > 100 μM.[16] Boer *et al.*,[17] in their studies of the hypotensive effect of propofol during cardiopulmonary bypass, suggested that the hypotensive effect of propofol was not related to a reduction in sympathetic outflow but rather was related to a direct arterial vasodilation because plasma catecholamine concentration was not changed during administration of propofol. A clinical baroreflex study also suggested a direct inhibition of vascular smooth muscle activity through a consistent and significant decrease of the diastolic overshoot after a Valsalva maneuver, which reflects a direct target organ depression by propofol.[18] An absence of ganglionic blocking or α-adrenoreceptor antagonistic properties of propofol has also been suggested.[19] The current results confirm these previous findings that suggested a direct vasodilating action of propofol without the necessity for alteration in sympathetic outflow. Nevertheless, altered sympathetic tone has been observed clinically and may contribute to propofol's effect.[20]

The effects of propofol on the pulmonary artery are controversial. Claeys *et al.*[21] reported that immediately after the induction of unconsciousness after propofol administration, pulmonary vascular resistance increased transiently by 36%, but returned to normal and was maintained during the infusion. Systemic hypotension was not accompanied by pulmonary arterial hypotension. Others also implied that propofol neither influences pulmonary vascular tone nor inhibits hypoxic pulmonary vasoconstriction.[22] However, our results demonstrate that propofol is a direct and potent pulmonary artery vasodilator. Recently, Rouby *et al.*[23] reported a significant pulmonary artery vasodilating effect of propofol in their studies in humans with artificial hearts, consistent with the observed vasodilating effects of propofol on the pulmonary arteries in our studies.

Previous studies on the hemodynamic effects of thiopental have shown that a decrease in arterial pressure after administration of thiopental is caused by a decrease in cardiac output associated with decreased,[2] unchanged,[24] or slightly increased[25,26] systemic vascular resistance. A variety of actions of thiopental on vasculature have been described. Thiopental enhanced contractions induced by norepinephrine in rabbit aortic[27] and pulmonary artery strips,[28] which suggested an increased responsiveness of the α-adrenergic receptor to sympathetic stimulation. In contrast, Altura and Altura[29] found that 250 μM thiopental depressed epinephrine-induced contractions in isolated rat aorta and portal vein. However, 100 μM thiopental did not inhibit the tension in aortic smooth muscle, although it depressed the portal vein tension by about 55%. Fukuda *et al.*[28] suggested that the different responses of rabbit and rat aortic strips to thiopental may be due to the specific α receptors of the rat aorta, which closely resemble an α_2 subtype,[30] different from that found in other mammalian aortas.

Our results, in which 10, 30, and 100 μM thiopental did not elicit any vascular response, are compatible with Altura and Altura's findings.[29] These concentrations represent relevant clinical free drug concentrations, because anesthetic serum concentrations (13–93 μg/ml, or 48–352 μM) should yield free thiopental levels of 7.2–60 μM, assuming 83–86% protein binding.[31,32] Although our results show negligible arterial effects of thiopental *in vitro*, it is difficult to predict the *in vivo* results because of thiopental's influence on sympathetic activity. Skovsted *et al.*[33] reported that thiopental inhibited sympathetic nervous activity in cats by inhibiting pressor neurons in the medulla oblongata, whereas the medullary depressor neurons were relatively unaffected. These findings suggested that thiopental caused greater inhibition of central sympathetic nervous activity than parasympathetic nervous activity. Therefore it is likely that some effects of thiopental on peripheral vascular resistance *in vivo* and in clinical circumstances may be centrally mediated. Whereas no direct vasodilation was seen with thiopental in the current study, Coughlan *et al.*[16] found that like propofol, low concentrations of thiopental (≥ 5 μM) caused relaxation of distal canine coronary arteries, whereas relaxation in proximal coronary arteries occurred only at higher concentrations (~ 500 μM). These differing results in vessels of varying caliber also contrast with the current work, suggesting that particular vascular beds (and perhaps particular species) may produce distinctive responses to these agents.

EDRF is a potent vasodilator produced by the endothelium under basal conditions and in response to a variety of agonists. It diffuses from the endothelium to the underlying vascular smooth muscle, where it causes relaxation through the activation of soluble guanylate cyclase,

causing an increase in 3',5'-cyclic guanosine monophosphate.[34] EDRF is produced from L-arginine by the calcium-, calmodulin-, and NADPH-dependent enzyme EDRF/NO synthase,[35] which is inhibited by specific analogues of L-arginine such as LNAME, as used in this study.[10] In intact vessels, 30 and 100 μM propofol caused an initial maximum vasodilation followed an increase in tension toward the preconstricted level, an effect not observed in endothelium-denuded and LNAME-pretreated vascular rings. The return toward baseline force in intact vessels resulted in less profound relaxation than in the denuded vessels.

The discrepancies in vasodilation between endothelium-intact and -denuded rings at the end of propofol administration clearly implicate endothelium as responsible for this late phenomenon. This late relative constriction may be explained in two ways: 1) basal EDRF production is inhibited; or 2) some vasoconstricting agent is stimulated and released to the vascular smooth muscle from the endothelium. The response is most likely due to the inhibition of EDRF, because endothelium-intact vessels pretreated with the specific EDRF inhibitor, LNAME, exhibited sustained vasodilation to propofol stimulation. If EDRF/NO synthase is already maximally inhibited by LNAME, no further inhibition of EDRF synthesis by propofol resulting in constriction should occur, as was observed. In intact vessels, the ongoing basal EDRF synthesis decreases the maximal force and increases the phenylephrine EC_{50} (fig. 1). When such EDRF synthesis is inhibited by propofol, the resulting vasoconstriction will counteract the direct vasodilating action of propofol, resulting in a smaller degree of vasodilation in the intact vessels. Because endothelin also stimulates EDRF production,[36] the data by Coughlan *et al.*,[16] which showed that low concentrations of propofol increased endothelin-induced tone in coronary vessels, would be explained by such a decrease in EDRF production by propofol.

Thiopental significantly enhanced vasoconstriction in endothelium-intact vascular rings when the cyclooxygenase activity was blocked by indomethacin pretreatment, whereas propofol caused less vasodilation under the same conditions. In either case, the greater tension seen with indomethacin could result from blockade of production of vasodilating prostaglandins that had been induced by the anesthetics. Prostacyclin (prostaglandin I_2), an end product of the cyclooxygenase pathway, is known to be a potent vasodilator, and the endothelium is a principal source of prostacyclin.[37] In the rabbit aorta there is a progressive decrease in generation of prostacyclin from the intima surface to the adventitia,[38] with at least a 10-fold greater conversion of prostaglandin H_2 to prostaglandin I_2 in the intimal layer compared to the media and adventitia.[39] If propofol and thiopental modestly activated prostaglandin I_2 synthase, inhibition of its activity by indomethacin would explain the diminished relaxation or vasoconstriction that occurs with propofol and thiopental in the presence of indomethacin.

In summary, this study demonstrated markedly different vascular actions of propofol and thiopental. Propofol caused significant vasodilation in aortic and pulmonary artery rings, whereas thiopental had no effect. While the initial maximum vasodilation by propofol was probably due to a direct vasodilating action on the vascular smooth muscle, attenuation of vasodilation at the end of propofol administration may be related to the inhibition of EDRF production. Indomethacin caused significant potentiation of endothelium-dependent vasoconstriction with thiopental and produced a decrease in propofol-induced dilation, consistent with propofol and thiopental induction of vasodilating cyclooxygenase metabolites in endothelium-intact aortic preparations.

The authors thank Alexandra Tichotsky for technical assistance and Martha J. Frazer and Dr. Joseph J. Pancrazio for helpful review and discussion.

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