Anesthesiology 2001; 94:815–23

Pulmonary Vascular Effects of Propofol at Baseline, during Elevated Vasomotor Tone, and in Response to Sympathetic α- and β-Adrenoreceptor Activation

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Background: **This *in vivo* study had two primary objectives. The first goal was to determine whether the pulmonary vascular effects of propofol depend on the preexisting level of vasomotor tone, and the second was to investigate the effects of propofol on the pulmonary vascular responses to sympathetic α- and β-adrenoreceptor activation.**

Methods: **Thirty-one mongrel dogs were chronically instrumented to measure the left pulmonary vascular pressure–flow (LPQ) relation. Left lung autotransplantation (LLA) was also performed in eight additional dogs to induce a long-term increase in pulmonary vascular resistance. LPQ plots were measured on separate days in the conscious state and during propofol anesthesia. LPQ plots were measured at baseline and when vasomotor tone was acutely increased with the α agonist, phenylephrine, or the thromboxane mimetic, U46619. In separate experiments, cumulative dose–response curves to α- (phenylephrine) and β- (isoproterenol) adrenoreceptor agonists were generated in conscious and propofol-anesthetized dogs.**

Results: **Compared with the conscious state, propofol had no effect on the baseline LPQ relation in normal or post-LLA dogs. However, propofol caused pulmonary vasoconstriction ($P < 0.05$) when vasomotor tone was acutely increased with either phenylephrine or U46619 in normal or post-LLA dogs. The pulmonary vasoconstrictor response to α-adrenoreceptor activation was potentiated ($P < 0.05$) during propofol anesthesia, whereas the pulmonary vasodilator response to β-adrenoreceptor activation was not altered.**

Conclusion: **These results indicate that the pulmonary vascular response to propofol anesthesia is tone-dependent. During sympathetic activation, propofol may favor α-adrenoreceptor–mediated vasoconstriction over β-adrenoreceptor–mediated vasodilation.**

THE pulmonary circulation is the afterload against which the right ventricle must eject blood. Because of the relatively limited contractile reserve of the right ventricle, it is important to evaluate the effects of anesthetic agents and cardiovascular drugs on pulmonary vasoregulation. We recently reported that propofol anesthesia has no effect on the baseline pulmonary vascular pressure–flow relation in chronically instrumented dogs, whereas it potentiates the magnitude of hypoxic pulmonary vasoconstriction.[1] Propofol is often used in patients during periods of cardiovascular stress (*e.g.*, surgery or postoperative sedation), when vasomotor tone may be increased. We are not aware of any study that has systematically assessed the effects of propofol on the intact pulmonary circulation in the setting of elevated vasomotor tone or during sympathetic adrenoreceptor activation. The first goal of the current study was to test the hypothesis that the pulmonary vascular effects of propofol depend on the preexisting level of vasomotor tone. To investigate this, we used chronically instrumented dogs in which pulmonary vasomotor tone could be acutely increased with the α-adrenoreceptor agonist, phenylephrine, or the thromboxane mimetic, U46619. We also assessed the effects of propofol in an experimental model of left lung autotransplantation (LLA), which we have previously demonstrated results in a long-term increase in pulmonary vascular resistance.[2] Our second goal was to test the hypothesis that propofol anesthesia alters the pulmonary vascular response to sympathetic α- and β-adrenoreceptor activation. Specifically, we hypothesized that propofol would potentiate the pulmonary vasoconstrictor response to α-adrenoreceptor activation, whereas it would attenuate the pulmonary vasodilator response to β-adrenoreceptor activation.

Material and Methods

All surgical procedures and experimental protocols were approved by the Institutional Animal Care and Use Committee of The Cleveland Clinic Foundation.

Surgery for Chronic Instrumentation

Thirty-one conditioned mongrel dogs weighing 20–30 kg were used in these studies. The surgery for chronic instrumentation has been described in detail.[3] Briefly, all dogs were anesthetized, intubated, and mechanically ventilated. Using sterile surgical technique, a left lateral thoracotomy was performed *via* the fifth intercostal space. The pericardium was incised ventral to the phrenic nerve. Heparin-filled Tygon catheters (1.02-mm ID; Norton, Akron, OH) were inserted into the descending thoracic aorta, main pulmonary artery, and right and left atrium. The catheters were secured with purse-string sutures. A hydraulic occluder (18-mm ID; In Vivo Metric, Healdsburg, CA) was loosely positioned around the right main pulmonary artery. An electromagnetic flow probe (10-mm ID; Zepeda, Seattle, WA) was placed around the left main pulmonary artery. The pericardial edges were loosely apposed. The catheters, occluder, and flow

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Received from the Center for Anesthesiology Research, Division of Anesthesiology and Critical Care Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio. Submitted for publication July 21, 2000. Accepted for publication November 14, 2000. Supported by grants No. HL-38291 and HL-40361 from the National Heart, Lung and Blood Institute, Bethesda, Maryland. Dr. Kondo was supported by Professor Yasuhiro Shimada, M.D., Ph.D., Department of Anesthesiology, Nagoya University School of Medicine, Nagoya, Japan.

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probe were threaded through the seventh intercostal space and then tunneled subcutaneously to a final position between the scapulae. A chest tube placed in the left thorax before closure was removed the next day. Analgesics were administered postoperatively for pain as required. Antibiotics were administered intravenously during surgery and on a daily basis for 10 days postoperatively. Experiments were not performed until at least 2 weeks after the surgery to allow the dogs to recover and become acclimated to the laboratory environment.

Surgery for Left Lung Autotransplantation

The surgical technique for LLA has been described in detail.[2] Eight dogs underwent LLA *via* sequential divisions and anastomoses of the left pulmonary veins, left mainstem bronchus, and left main pulmonary artery. A wide circumhilar pericardial incision mobilized the left lung. After administering 3,000 units of heparin intravenously, the inferior, middle, and superior pulmonary veins were individually dissected to their point of confluence with the left atrium. The veins were cross-clamped, divided, and anastomosed with a continuous stitch of 7-0 Prolene suture. The left mainstem bronchus was clamped distal to the carina, divided, and anastomosed using a continuous stitch of 4-0 Prolene suture. The left main pulmonary artery was isolated, cross-clamped, divided, and anastomosed with a continuous stitch of 6-0 Prolene suture. The cross-clamp time for the left pulmonary artery was approximately 15 min. Care was taken to avoid air emboli and luminal narrowing and to ensure good intimal apposition at the anastomotic sites. Aside from the LLA procedure, the chronic instrumentation and postoperative care were identical to that described in the preceding section.

Experimental Measurements

As described in detail previously,[3] vascular pressures were measured by attaching the fluid-filled catheters to strain-gauge manometers (Isotec, Quest Medical, Allen, TX). Vascular pressures were referenced to atmospheric pressure with the transducers positioned at midchest at the level of the spine. Left pulmonary blood flow (LQ) was measured by connecting the flow probe to an electromagnetic flowmeter (SWF-5RD, Zepeda). The flow probe was calibrated *in vivo* on a weekly basis by the thermal dilution technique.[3] The aortic and pulmonary artery catheters were used to obtain blood gases (ABL-600, Radiometer, Copenhagen, Denmark) and oxyhemoglobin saturation (OSM-3, Radiometer).

Experimental Protocols

All experiments were performed with each healthy, chronically instrumented dog lying on its right side in a quiet laboratory environment. Conscious dogs were not sedated. Muscle relaxants were not used during propofol anesthesia. The effects of the various experimental interventions on the pulmonary circulation were assessed by measuring changes in the left pulmonary vascular pressure–flow (LPQ) relation. LPQ plots were generated by continuously measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure–left atrial pressure [PAP-LAP]) and LQ during gradual (approximately 1 min) inflation of the hydraulic occluder implanted around the right main pulmonary artery. This technique to measure the LPQ relation is highly reproducible and has little or no effect on systemic hemodynamics, blood gases, or the zonal condition of the lung.[3]

Protocol 1: Effects of Propofol Anesthesia on the Left Pulmonary Vascular Pressure–Flow Relation at Baseline and During Elevated Pulmonary Vasomotor Tone. We tested the hypothesis that the pulmonary vascular effects of propofol anesthesia are tone-dependent. We previously demonstrated that propofol anesthesia has no effect on the baseline LPQ relation.[1] To confirm this, a baseline LPQ plot was first obtained in the conscious state (n = 8 dogs). Anesthesia was then induced by an intravenous bolus injection of 5.0 mg/kg propofol. An endotracheal tube was placed, and ventilation was controlled with a respirator with zero end-expiratory pressure. Immediately after intubation, propofol was administered intravenously as a continuous infusion (0.5 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}). This dose of propofol results in a surgical plane of anesthesia in dogs. Tidal volume was fixed at 15 ml/kg. Systemic arterial blood gas values were matched to values measured in the conscious state by administering supplemental oxygen (fractional inspiratory oxygen = 0.26) and by adjusting the respiratory rate to 10–20 breaths/min. End-tidal carbon dioxide and oxygen tensions were monitored continuously at the adapter end of the endotracheal tube throughout the experiment (Solar 7000; Marquette Electronics, Milwaukee, WI). After induction, propofol was allowed to equilibrate for 30 min to achieve steady state conditions. An LPQ plot was then generated during propofol anesthesia.

On a separate day, we assessed the effects of propofol anesthesia on the LPQ relation after increasing pulmonary vasomotor tone with the α-adrenoreceptor agonist, phenylephrine (n = 5 dogs). LPQ plots were generated in the conscious state at baseline, after β-adrenoreceptor inhibition with propranolol (1 mg/kg intravenously) to inhibit the β-agonist effects of phenylephrine, and when pulmonary vasomotor tone was increased with phenylephrine (0.75 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} administered intravenously). Anesthesia was then induced with propofol as described in the preceding section. After a 30-min equilibration period, an LPQ plot was generated during propofol anesthesia.

We also assessed the effects of propofol anesthesia on the LPQ relation after increasing pulmonary vasomotor tone with the thromboxane mimetic, U46619 (n = 8 dogs). LPQ plots were generated in the conscious state

at baseline and when pulmonary vasomotor tone was increased with U46619 (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ administered intravenously). Anesthesia was then induced with propofol. An LPQ plot was constructed 30 min later during propofol anesthesia.

Finally, we assessed the effects of propofol anesthesia on the LPQ relation in a group of eight dogs that had undergone LLA approximately 30 days earlier. We previously demonstrated that LLA results in a long-term increase in pulmonary vascular resistance.[2] LPQ plots were generated in the conscious state at baseline, and then during the cumulative intravenous administration of propofol (5 mg/kg bolus dose plus 0.25-, 0.5-, and 1.0-mg $\cdot kg^{-1} \cdot min^{-1}$ infusion). On a separate day, each post-LLA dog was studied after acutely increasing pulmonary vasomotor tone with U46619 (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ administered intravenously). LPQ plots were obtained in the conscious state at baseline and when pulmonary vasomotor tone was acutely increased with U46619. Anesthesia was then induced with propofol. LPQ plots were generated during the cumulative intravenous administration of propofol, as described above.

Protocol 2: Effect of Propofol Anesthesia on the Pulmonary Vascular Response to Sympathetic α-Adrenoreceptor Activation. We tested the hypothesis that the pulmonary vasoconstrictor response to the α agonist, phenylephrine, is potentiated during propofol anesthesia. In the conscious state (n = 8 dogs), LPQ plots were generated at baseline, after β-adrenoreceptor inhibition with propranolol (1 mg/kg administered intravenously), and during the cumulative intravenous administration (approximately 15 min at each dose) of phenylephrine (0.01–1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$). This experiment was repeated on a separate day in the same dogs during propofol anesthesia (5 mg/kg plus 0.5 mg $\cdot kg^{-1} \cdot min^{-1}$ administered intravenously).

Protocol 3: Effect of Propofol Anesthesia on the Pulmonary Vascular Response to Sympathetic β-Adrenoreceptor Activation. We tested the hypothesis that the pulmonary vasodilator response to the β agonist, isoproterenol, is attenuated during propofol anesthesia. In the conscious state (n = 8 dogs), LPQ plots were generated at baseline, after preconstriction with U46619, and during the cumulative intravenous administration (approximately 15 min at each dose) of isoproterenol (0.01–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The dose of U46619 was titrated to achieve an approximate doubling of PAP-LAP from baseline values at a given level of LQ. LPQ plots were obtained during preconstriction with U46619 alone and then at each dose of isoproterenol while the infusion of U46619 was continued. We have previously demonstrated that pulmonary vasoconstriction induced by U46619 is stable during the time course of this protocol.[4] On a different day, this experiment was repeated in the same dogs during propofol anesthesia (5 mg/kg plus 0.5 mg $\cdot kg^{-1} \cdot min^{-1}$ administered intravenously). During propofol anesthesia, the dose of U46619 was carefully titrated to achieve the same degree of preconstriction induced in the conscious state. The titration procedure involved administering incremental doses of U46619 and generating LPQ plots until a dose was found that caused the same degree of preconstriction that was achieved in the conscious state. This allowed us to compare the magnitude of the pulmonary vasodilator response to isoproterenol at the same level of vasomotor tone in the conscious and propofol-anesthetized states.

Drug Preparation

All solutions were prepared on the day of the experiment. Propranolol (Sigma Chemical, St. Louis, MO) was dissolved in sterile water. Phenylephrine and isoproterenol (Elkins-Sinn, Cherry Hill, NJ), as well as U46619 (a gift from Cayman Chemical, Ann Arbor, MI), were diluted in 0.9% saline. Propofol was purchased from AstraZeneca Pharmaceuticals (Wilmington, DE). We have previously demonstrated that the intralipid emulsion diluent for propofol has no effect on the LPQ relation.[1]

Data Analysis

Phasic and mean vascular pressures and LQ were displayed continuously on an eight-channel strip-chart recorder (2800; Gould, Eastlake, OH). Mean pressures and LQ, measured at end expiration, were obtained with the use of passive electronic filters with a 2-s time constant. All vascular pressures were referenced to atmospheric pressure before and after each LPQ plot. The analog pressure and LQ signals were digitally converted and multiplexed (PCM-8; Medical Systems, Greenvale, NY) and stored on videotape (videocassette recorder AG-1260; Panasonic, Secaucus, NJ) for later playback and analysis. The LPQ relation was measured continuously over the empirically measured range of LQ in each individual experiment. In all protocols, the LPQ relation was linear by inspection over the empirically measured range of LQ. Therefore, linear regression analysis was used to calculate the slope and intercept for PAP-LAP (or PAP-0 if LAP was $\leq$ 0 mmHg) as a function of LQ in each individual experiment. The correlation coefficient for the LPQ relation in each protocol averaged 0.98 or higher. The composite LPQ plots summarized in the figures were generated using the regression parameters from each individual continuously measured LPQ plot to calculate PAP-LAP at 10-ml $\cdot min^{-1} \cdot kg^{-1}$ intervals of LQ over the empirically measured range of LQ. The minimum and maximum values of LQ in each composite LPQ plot represent the average minimum and maximum values of LQ for the dogs studied in that protocol. The pulmonary vasoconstrictor response to phenylephrine is expressed as the increase in PAP-LAP from baseline at LQ = 80 ml $\cdot min^{-1} \cdot kg^{-1}$ in response to the cumulative administration of phenylephrine. The pulmonary vasodi-

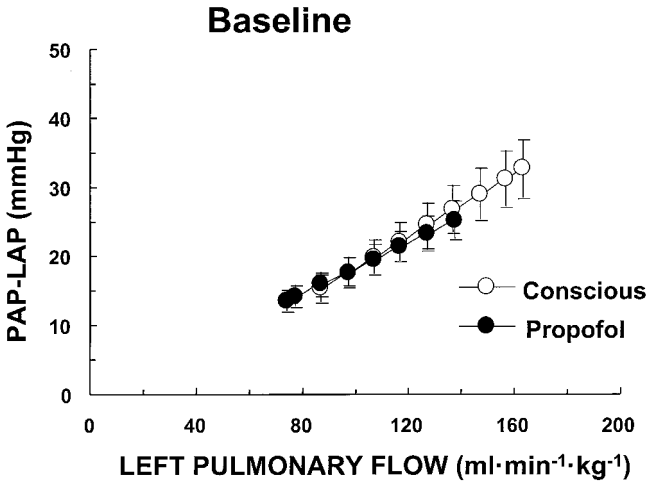

Fig. 1. Composite left pulmonary vascular pressure–flow plots measured in the same dogs (n = 8) in the conscious state and during propofol anesthesia. Compared with the conscious state, propofol had no effect on the baseline left pulmonary vascular pressure–flow relation. PAP-LAP = pulmonary arterial pressure–left atrial pressure.

lator response to isoproterenol is expressed as the percentage decrease in U46619 preconstriction at LQ = 80 ml · min^{-1} · kg^{-1} and was calculated as follows:[3]

$$\frac{(\text{PAP-LAP})_{\text{U46619}} - (\text{PAP-LAP})_{\text{isoproterenol}}}{(\text{PAP-LAP})_{\text{U46619}} - (\text{PAP-LAP})_{\text{baseline}}} \times 100 \quad (1)$$

Thus, a vasodilator-induced decrease in PAP-LAP of 100% represents a complete reversal of U46619 preconstriction and a full return to the baseline LPQ relation. One-way analysis of variance followed by the Student *t* test for paired comparisons was used to assess the pulmonary vascular effects of each intervention within each group. Two-way analysis of variance followed by the Student *t* test for paired comparisons was used to assess the effects of propofol anesthesia on the magnitude of the agonist-induced pulmonary vascular responses. All values are presented as mean ± SEM.

Results

Protocol 1: Effects of Propofol Anesthesia on the Left Pulmonary Vascular Pressure–Flow Relation at Baseline and During Elevated Pulmonary Vasomotor Tone

We tested the hypothesis that the pulmonary vascular effects of propofol are tone-dependent. As we previously reported,[1] propofol had no effect on the baseline LPQ relation compared with the conscious state (fig. 1). In the conscious state, propranolol had no effect on the baseline LPQ relation (fig. 2A). Phenylephrine caused a leftward shift in the LPQ relation, indicating pulmonary vasoconstriction (fig. 2B). In the presence of this phenylephrine-induced increase in pulmonary vasomotor tone, the administration of propofol resulted in pulmonary vasoconstriction (fig. 2B). In a similar manner, after U46619 preconstriction, propofol again caused pulmonary vasoconstriction (fig. 3). Compared with normal conscious dogs, the LPQ relation is leftward shifted in conscious dogs 1 month after LLA, indicating a long-term increase in pulmonary vascular resistance (fig. 4). Propofol had no effect on the baseline LPQ relation in post-LLA dogs (fig. 5). However, propofol caused pulmonary vasoconstriction in the presence of U46619 preconstriction in post-LLA dogs (fig. 6). The propofol dose–response relation in post-LLA dogs in the no-drug condition and after U46619 preconstriction is summarized in figure 7. Propofol had no effect on LLA dogs without U46619 preconstriction, whereas it caused dose-dependent pulmonary vasoconstriction after pretreatment with U46619 (fig. 7).

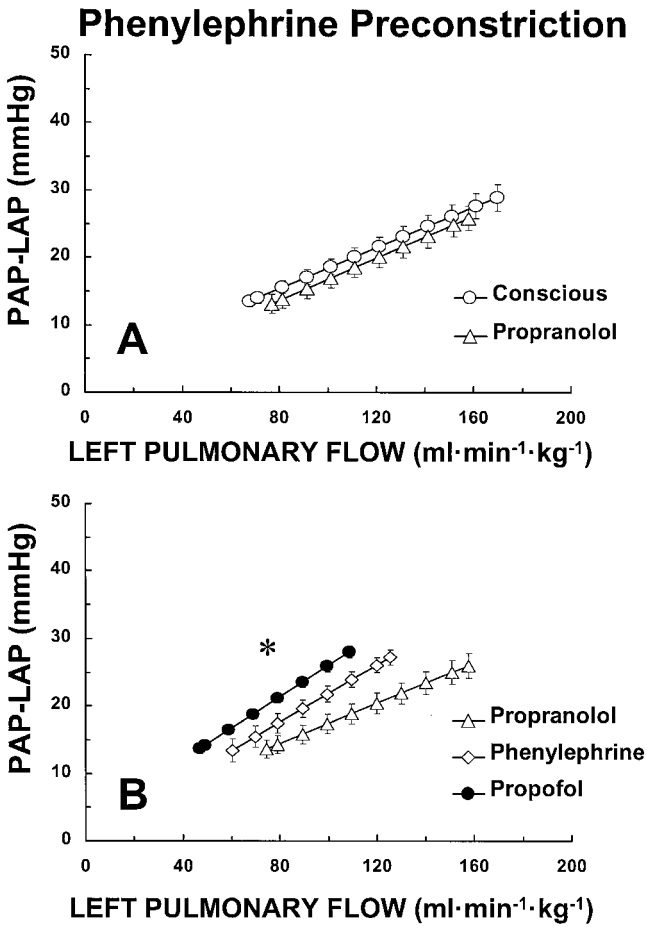

Fig. 2. (*A*) Composite left pulmonary vascular pressure–flow plots measured in conscious dogs (n = 5) at baseline and after β-adrenoreceptor inhibition with propranolol. Propranolol had no effect on the baseline left pulmonary vascular pressure–flow relation. (*B*) Composite left pulmonary vascular pressure–flow plots measured in the conscious state after propranolol pretreatment, when vasomotor tone was acutely increased with phenylephrine, and during propofol anesthesia. Propofol caused pulmonary vasoconstriction (*$P < 0.05$) when vasomotor tone was increased with phenylephrine. PAP-LAP = pulmonary arterial pressure–left atrial pressure.

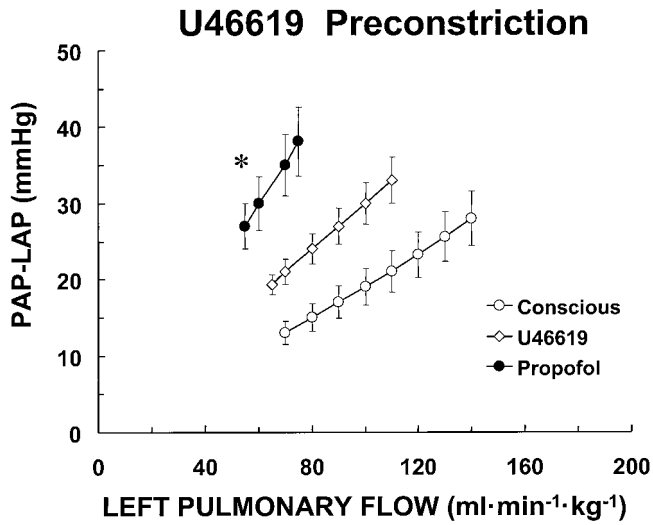

Fig. 3. Composite left pulmonary vascular pressure–flow plots measured in the conscious state (n = 8), when vasomotor tone was acutely increased with U46619, and during propofol anesthesia. Propofol caused pulmonary vasoconstriction (*$P < 0.05$) when vasomotor tone was increased with U46619. PAP-LAP = pulmonary arterial pressure–left atrial pressure.

Protocol 2: Effect of Propofol Anesthesia on the Pulmonary Vascular Response to Sympathetic α-Adrenoreceptor Activation

We tested the hypothesis that the pulmonary vasoconstrictor response to the α agonist, phenylephrine, is potentiated during propofol anesthesia. The phenylephrine dose–response relation in the conscious state and during propofol anesthesia after β-adrenoreceptor block with propranolol is summarized in figure 8. The magnitude of phenylephrine-induced pulmonary vasoconstriction was either preserved or potentiated during propofol anesthesia (fig. 8).

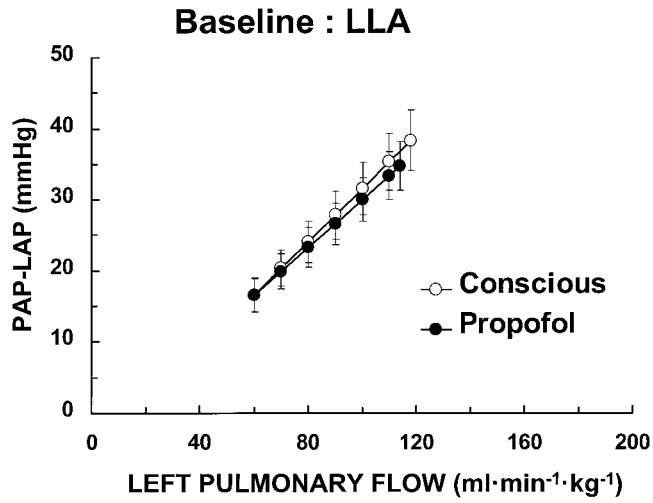

Fig. 5. Composite left pulmonary vascular pressure–flow plots after left lung autotransplantation (LLA) in dogs (n = 8) in the conscious state and during propofol anesthesia. Compared with the conscious state, propofol had no effect on the baseline left pulmonary vascular pressure–flow relation after LLA. PAP-LAP = pulmonary arterial pressure–left atrial pressure.

Protocol 3: Effect of Propofol Anesthesia on the Pulmonary Vascular Response to Sympathetic β-Adrenoreceptor Activation

We tested the hypothesis that the pulmonary vasodilator response to the β agonist, isoproterenol, is attenuated during propofol anesthesia. U46619 was used to preconstrict the pulmonary circulation before the administration of isoproterenol. The dose of U46619 was titrated to achieve the same degree of preconstriction in

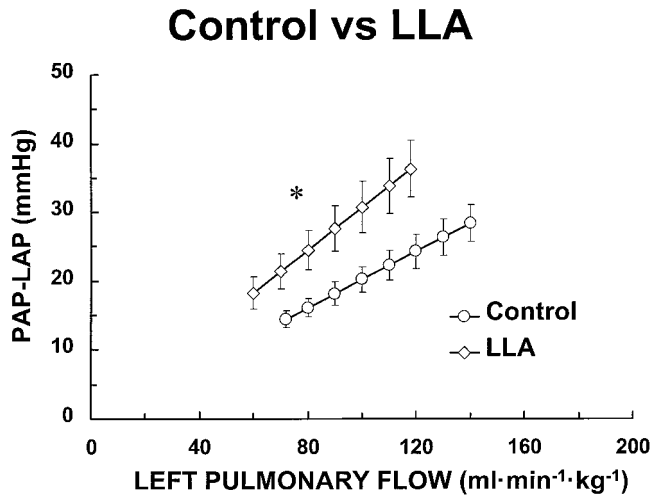

Fig. 4. Composite left pulmonary vascular pressure–flow plots in the conscious state in control sham-operated dogs (n = 8) and in conscious dogs (n = 8) approximately 30 days after left lung autotransplantation (LLA). Compared with control dogs, LLA resulted in a long-term increase (*$P < 0.05$) in pulmonary vascular resistance. PAP-LAP = pulmonary arterial pressure–left atrial pressure.

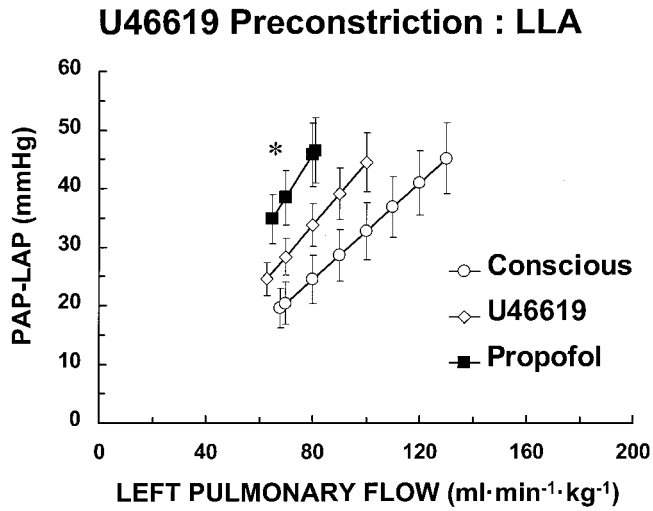

Fig. 6. Composite left pulmonary vascular pressure–flow plots after left lung autotransplantation (LLA; n = 8) in the conscious state, after preconstriction with U46619, and during propofol anesthesia. Propofol caused pulmonary vasoconstriction (*$P < 0.05$) when vasomotor tone was increased with U46619. PAP-LAP = pulmonary arterial pressure–left atrial pressure.

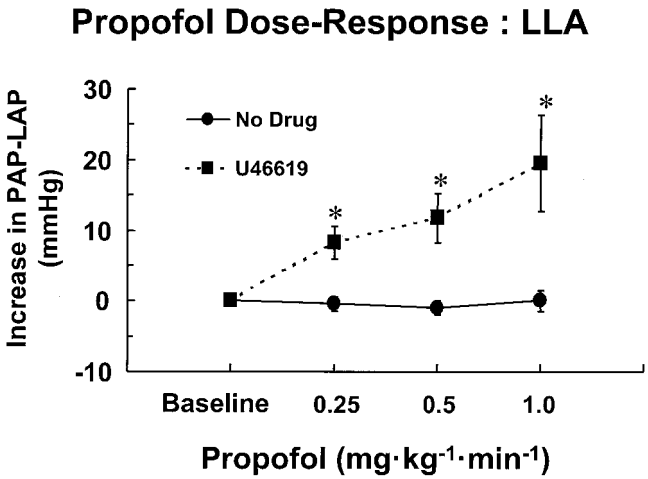

Fig. 7. Propofol dose–response relationship after left lung autotransplantation (LLA; n = 8) on separate days without preconstriction (no drug) and after preconstriction with U46619. Increases in the pulmonary vascular pressure gradient (PAP-LAP) at left pulmonary blood flow = 80 ml · min^{-1} · kg^{-1} in response to the cumulative administration of propofol are summarized. Propofol had no effect on the left pulmonary vascular pressure–flow relation in the no-drug condition, whereas it caused dose-dependent pulmonary vasoconstriction (*P < 0.05) in the setting of U46619 preconstriction.

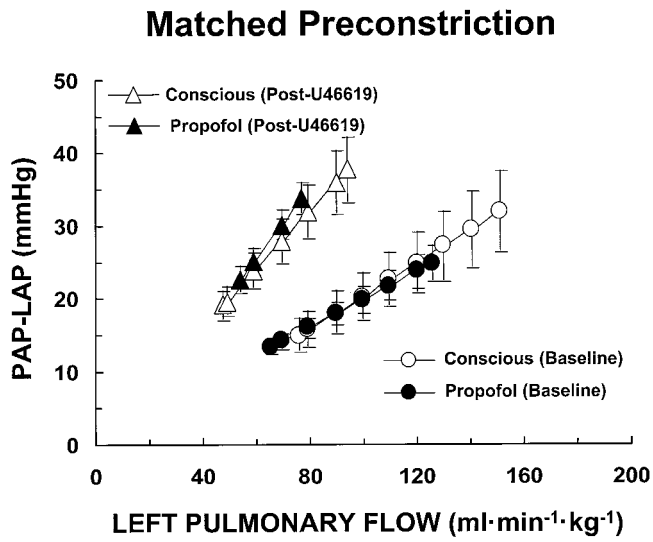

Fig. 9. Composite left pulmonary vascular pressure–flow plots at baseline and after preconstriction with U46619 in the conscious state and during propofol anesthesia. The dose of U46619 is titrated to achieve the same degree of preconstriction in the conscious and propofol-anesthetized states. PAP-LAP = pulmonary arterial pressure–left atrial pressure.

the conscious and propofol-anesthetized states (fig. 9). The isoproterenol dose–response relation in the conscious state and during propofol anesthesia after U46619 preconstriction is summarized in figure 10. Isoproterenol-induced pulmonary vasodilation was not altered during propofol anesthesia compared with the conscious state.

Systemic Hemodynamics and Blood Gases

In general, there were very few changes in systemic hemodynamics or blood gases. In control dogs without preconstriction, propofol decreased ($P < 0.05$) mean systemic arterial pressure and had no effect on systemic arterial or mixed venous blood gases (table 1). In control conscious dogs, propranolol decreased ($P < 0.05$) heart rate to 80 ± 5 beats/min. In dogs pretreated with propranolol, phenylephrine increased ($P < 0.05$) systemic arterial pressure to 132 ± 11 mmHg. Neither propranolol nor phenylephrine had an effect on blood gases. In

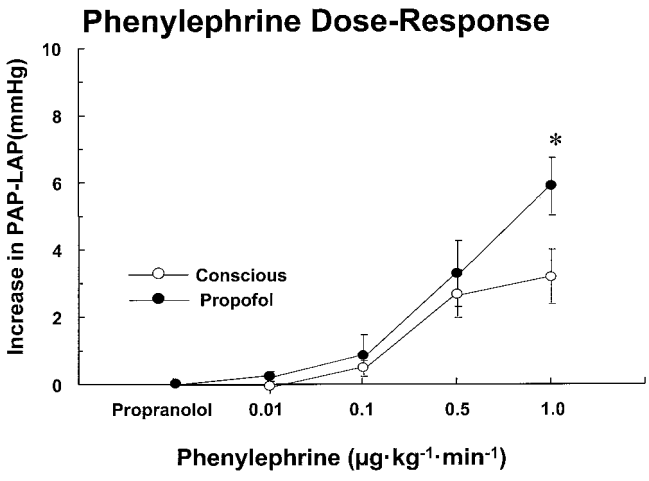

Fig. 8. Phenylephrine dose–response relation in the conscious state and during propofol anesthesia after β-adrenoreceptor block with propranolol. Increases in the pulmonary vascular pressure gradient (PAP-LAP) at left pulmonary blood flow = 80 ml · min^{-1} · kg^{-1} in response to the cumulative administration of phenylephrine are summarized. The magnitude of phenylephrine-induced pulmonary vasoconstriction is either preserved or potentiated (*P < 0.05) during propofol anesthesia.

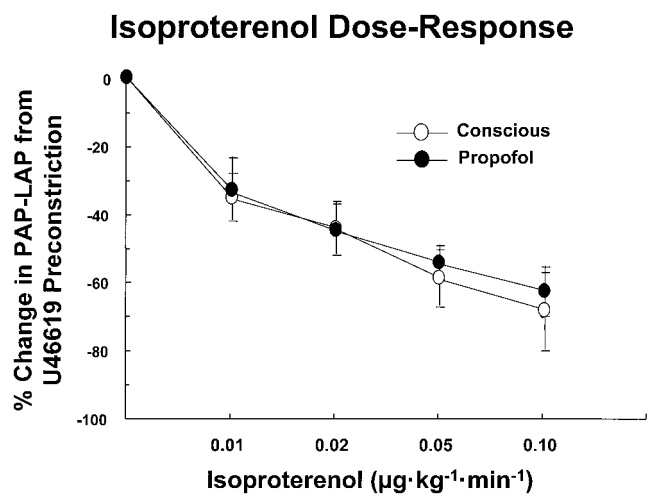

Fig. 10. Isoproterenol dose–response relation in the conscious state and during propofol anesthesia after U46619 preconstriction. Vasodilator response to isoproterenol is expressed as the percentage decrease in U46619 preconstriction. Isoproterenol-induced pulmonary vasodilation is similar in the conscious and propofol-anesthetized states. PAP-LAP = pulmonary arterial pressure–left atrial pressure.

Table 1. Steady State Systemic Hemodynamics and Blood Gases

	Control		LLA	
Hemodynamics	Conscious	Propofol	Conscious	Propofol
SAP (mmHg)	91 ± 6	83 ± 4*	96 ± 3	92 ± 4
HR (beats/min)	96 ± 7	105 ± 10	95 ± 7	108 ± 8
Systemic arterial				
pH	7.40 ± 0.01	7.40 ± 0.01	7.40 ± 0.01	7.39 ± 0.01
P_{CO_2} (mmHg)	39 ± 2	39 ± 1	37 ± 1	38 ± 1
P_{O_2} (mmHg)	94 ± 3	91 ± 5	98 ± 2	91 ± 3
S_{O_2} (%)	97 ± 1	96 ± 1	97 ± 1	96 ± 1
Mixed venous				
pH	7.37 ± 0.01	7.38 ± 0.01	7.37 ± 0.01	7.37 ± 0.01
P_{CO_2} (mmHg)	45 ± 1	44 ± 1	44 ± 1	42 ± 1
P_{O_2} (mmHg)	41 ± 1	40 ± 1	39 ± 1	41 ± 3
S_{O_2} (%)	68 ± 2	66 ± 3	65 ± 2	66 ± 3

* $P < 0.05$ propofol *versus* conscious.

LLA = left lung autotransplantation; SAP = mean systemic arterial pressure; HR = heart rate; P_{CO_2} = carbon dioxide tension; P_{O_2} = oxygen tension; S_{O_2} = oxyhemoglobin saturation.

phenylephrine-preconstricted dogs, propofol had no additional effect on systemic hemodynamics or blood gases. In conscious dogs, U46619 increased ($P < 0.05$) systemic arterial pressure to 110 ± 3 mmHg and decreased ($P < 0.05$) systemic arterial oxygen tension (83 ± 4 mmHg), oxygen saturation (94 ± 1%), and mixed venous oxygen saturation (58 ± 1%). In U46619-preconstricted dogs, propofol had no additional effect on systemic hemodynamics or blood gases. Compared with control conscious dogs, LLA had no effect on systemic hemodynamics or blood gases (table 1). Compared with conscious LLA dogs, propofol had no effect on systemic hemodynamics or blood gases (table 1), nor did propofol have any additional effect in the setting of U46619 preconstriction.

Discussion

The key results of this study are as follows. Propofol had no effect on the baseline LPQ relation in normal dogs but caused marked pulmonary vasoconstriction when vasomotor tone was acutely increased with phenylephrine or U46619. Propofol also had no effect on the baseline LPQ relation in post-LLA dogs, despite a long-term increase in pulmonary vascular resistance in this experimental model. Propofol caused dose-dependent pulmonary vasoconstriction in post-LLA dogs when vasomotor tone was acutely increased with U46619. Propofol potentiated the pulmonary vasoconstrictor response to sympathetic α-adrenoreceptor activation. Finally, propofol had no effect on the pulmonary vasodilator response to sympathetic β-adrenoreceptor activation.

Only a limited number of studies have directly assessed the effects of propofol on the pulmonary circulation. Propofol caused vasorelaxation in endothelium-intact, phenylephrine-precontracted rat pulmonary arterial rings.[5] Propofol also caused vasodilation in isolated perfused rat lungs precontracted with U46619,[6] KCl,[7] or angiotensin II.[8] In the study by Rich et al.,[8] a modest (8%) propofol-induced vasodilator response was reversed to a small (8%) vasoconstrictor response when the endothelium was injured with electrolysis, which suggests an endothelium-dependent mechanism is involved. However, nitric oxide or prostacyclin do not appear to mediate this endothelium-dependent response, because inhibiting their respective synthetic pathways had no effect on propofol-induced vasodilation.[6,7] There are conflicting reports concerning the role of adenosine triphosphate–sensitive K^+ channel activation in mediating propofol-induced pulmonary vasodilation.[6,7] Adenosine triphosphate–sensitive K^+ channel inhibition attenuated[7] or had no effect[6] on the pulmonary vasodilator response to propofol. Propofol also has been reported to cause vasodilation in isolated perfused rabbit lung precontracted with U46619.[9] Thus, propofol appears to exert a vasodilator influence in rat and rabbit lung, although the mechanism responsible for this effect has not been firmly established. In contrast, propofol had no effect on the baseline (no preconstriction) LPQ relation in either pentobarbital-anesthetized[10] or conscious[1] dogs, just as we observed in the current study. In human studies, propofol was reported to cause a transient (approximately 10-min) increase in pulmonary vascular resistance in elderly patients, although that effect was not sustained during the infusion of propofol.[11] In patients with an artificial heart and constant cardiac output, propofol had no statistically significant effect on pulmonary vascular resistance.[12] Thus, propofol does not appear to have a sustained effect on the baseline pulmonary circulation in either dogs or humans.

In contrast to baseline conditions, propofol caused marked pulmonary vasoconstriction when vasomotor tone was acutely increased with phenylephrine or

U46619. Phenylephrine-induced activation of α adrenoreceptors stimulates both phospholipase C[13] and phospholipase A_2.[14] Stimulation of these signaling pathways increases the release of arachidonic acid,[15–17] which is metabolized *via* the cyclooxygenase pathway to produce prostacyclin, thromboxane A_2, and other prostaglandins. U46619 also induces receptor-mediated activation of phospholipase C[18] and stimulates prostacyclin synthesis in the lung.[19] Because prostacyclin is a potent vasodilator, it could be postulated that propofol causes pulmonary vasoconstriction by inhibiting the synthesis or activity of prostacyclin during phenylephine- or U46619-induced precontraction. To test this hypothesis, we performed *in vitro* studies in isolated pulmonary arterial rings.[20] We observed that propofol had no effect on prostacyclin vasorelaxant activity but markedly reduced the synthesis of prostacyclin in response to α-adrenoreceptor activation.[20] These *in vitro* results support the concept that the pulmonary vasoconstrictor response to propofol *in vivo* is caused by an inhibitory effect of propofol on the endogenous release of prostacyclin that is stimulated by phenylephrine or U46619.

As we reported previously,[2] LLA resulted in a leftward shift in the LPQ relation, indicating a long-term increase in pulmonary vascular resistance. This experimental model is characterized by a number of abnormalities in pulmonary vascular regulation, including an enhanced pulmonary vasoconstrictor response to α-adrenoreceptor activation,[21] as well as attenuated vasodilator responses to β-adrenoreceptor activation[22,23] and endothelium-dependent agonists.[24,25] Because enhanced α-adrenoreceptor activity plays at least a partial role in the long-term increase in pulmonary vascular resistance,[21] we expected propofol to exert a pulmonary vasoconstrictor effect on the baseline LPQ relation in post-LLA dogs. However, propofol had no effect on the baseline LPQ relation and only caused dose-dependent vasoconstriction after preconstriction with U46619. We can only speculate that endogenous prostacyclin release is not chronically elevated post-LLA, despite the enhanced role of α-adrenoreceptor activation in regulating the baseline LPQ relation. This possibility is supported by our previous observation that cyclooxygenase pathway inhibition had no effect on the baseline LPQ relation after LLA.[26]

In the current study, propofol enhanced the pulmonary vasoconstrictor response to α-adrenoreceptor activation, whereas it had no effect on the vasodilator response to β-adrenoreceptor activation. To our knowledge, this is the first study to assess the effects of propofol on the pulmonary vascular responses to α- and β-adrenoreceptor activation. It seems likely that the enhanced response to phenylephrine is caused by the aforementioned inhibitory effect of propofol on endogenous prostacyclin release. This differential effect of propofol on α- and β-adrenoreceptor–mediated responses could have clinical implications. All else being equal, it would seem to suggest that during sympathetic activation (*e.g.*, surgery), propofol would favor α-mediated vasoconstriction over β-mediated vasodilation. Moreover, we have previously demonstrated that propofol enhances the magnitude of hypoxic pulmonary vasoconstriction.[1] Taken together, these effects of propofol could increase right ventricular afterload, which could have a deleterious effect in patients with right ventricular dysfunction. This effect could be even more important in patients with ischemic heart failure, where β adrenoreceptors are downregulated.[27] The extent to which propofol alters other factors (*e.g.*, elastance, wave reflection) that influence right ventricular afterload remains to be elucidated.

In summary, the pulmonary vascular response to propofol anesthesia is tone-dependent. During sympathetic activation, propofol may favor α-adrenoreceptor–mediated vasoconstriction over β-adrenoreceptor–mediated vasodilation.

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