Background: The objective was to investigate the effects of propofol anesthesia on the pulmonary vascular response to endothelium-dependent and -independent vasodilators, compared with the responses measured in the conscious state.

Methods: Twenty-six conditioned, male, mongrel dogs were instrumented long-term to measure the left pulmonary vascular pressure–flow relation. Pressure–flow plots were measured on separate days in conscious and propofol-anesthetized (5.0 mg/kg plus 0.5 mg kg\(^{-1}\) min\(^{-1}\) intravenously) dogs at baseline, after preconstriction with the thromboxane mimetic U46619, and during the cumulative intravenous administration of endothelium-dependent (acetylcholine and bradykinin) and -independent (proline–nitric oxide) vasodilators.

Results: Propofol had no effect on the baseline pressure–flow relation compared with the conscious state. A lower (P < 0.05) dose of U46619 was necessary to achieve the same degree of preconstriction during propofol anesthesia. The pulmonary vasodilator responses to bradykinin and proline–nitric oxide were similar in the conscious and propofol-anesthetized states. In contrast, the pulmonary vasodilator response to acetylcholine was markedly attenuated (P < 0.01) during propofol anesthesia. The intralipid vehicle for propofol had no effect on the acetylcholine dose–response relation.

Conclusion: These results suggest that propofol causes a specific defect in the signal transduction pathway for acetylcholine-induced pulmonary vasodilation. This defect involves the endothelial and not the vascular smooth muscle component of the response. (Key words: Endothelium-derived relaxing factors; lung; pulmonary circulation; vasomotor tone.)

PROPOFOL is a widely used intravenous anesthetic because of its rapid onset, short duration of action, and rapid elimination.\(^1\) We recently reported in long-term instrumented dogs that propofol has no effect on the baseline pulmonary vascular pressure–flow relation but causes profound pulmonary vasoconstriction in the setting of elevated vasomotor tone.\(^2\) The mechanism responsible for this effect is unknown. Propofol could directly increase pulmonary vascular smooth muscle tone.\(^3\) Alternatively, propofol could reduce the extent to which endothelium-dependent pulmonary vasodilation modulates the response to vasoconstrictor stimuli. In the current study, we tested this second possibility. Specifically, we tested the hypothesis that propofol attenuates endothelium-dependent pulmonary vasodilation. To our knowledge, this has not been previously evaluated in an intact animal model. We used two endothelial agonists (acetylcholine and bradykinin) to assess the effects of propofol on endothelium-dependent pulmonary vasodilation because these agonists have differential effects on the release of endothelium-derived mediators.\(^4\) We also used an ultrafast nitric oxide (NO) donor (proline–NO) to assess the integrity of the cyclic guanosine monophosphate signal transduction pathway in pulmonary vascular smooth muscle during propofol anesthesia.\(^5\)

Materials and Methods

All surgical procedures and experimental protocols were approved by the Institutional Animal Care and Use Committee of the Cleveland Clinic Foundation, Cleveland, Ohio.
Surgery for Long-term Instrumentation

Twenty-six conditioned male mongrel dogs (range, 23–33 kg; mean, 27 ± 1 kg) were used. All dogs were premedicated with morphine sulfate (10 mg intramuscularly) and were anesthetized with use of intravenous pentobarbital sodium (20 mg/kg) and fentanyl citrate (15 μg/kg). After tracheal intubation, the lungs were mechanically ventilated. Anesthesia was maintained with use of halothane (approximately 1.2% end-tidal). Using a 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 internal diameter; Norton, Akron, OH) were inserted into the descending thoracic aorta, left and right atria, and main pulmonary artery and were secured with purse-string sutures. After careful dissection and isolation, a hydraulic occluder (18 mm ID, In Vivo Metric, Healdsburg, CA) was positioned loosely around the right main pulmonary artery, and an electromagnetic flow probe (10 mm ID, Zepeda, Seattle, WA) was placed around the left main pulmonary artery. After loose apposition of the pericardial edges, the free ends of the catheters, occluder, and flow probe were threaded through the chest wall and were tunneled subcutaneously to a final position between the scapulae. A chest tube placed in the left thorax before closure was removed on postoperative day 1. Morphine sulfate (10 mg intramuscularly) was administered postoperatively for pain as necessary. Ampicillin (1 g), cefazolin (1 g), and gentamicin (80 mg) were administered intravenously during surgery and on a daily basis for 10 days postoperatively. The dogs were allowed to recover for at least 2 weeks before experiments were conducted.

Experimental Measurements

Vascular pressures were measured by attaching the fluid-filled catheters to strain-gauge manometers (Isopec, Quest Medical, Allen, TX), and were referenced to atmospheric pressure with the transducers positioned mid chest at the level of the spine. Heart rate was calculated from the phasic systemic arterial pressure (SAP) trace. 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 using the thermal dilution technique. Calibration was achieved by acutely inserting a 7-French balloon-tipped thermal dilution catheter into the pulmonary artery through a percutaneous jugular puncture after topical anesthesia. The catheter was positioned 2 to 3 cm beyond the pulmonic valve. The implanted perivascular hydraulic occluder was then inflated to completely occlude the right main pulmonary artery, which directed total pulmonary blood flow through the left pulmonary artery (and flow probe). LQ was then measured by thermal dilution (HEMOPRO2, Spectramed, Oxnard, CA) with multiple 10-ml sterile injections of 5% dextrose in water. Values for LQ were referenced to body weight (ml · min⁻¹ · kg⁻¹). The aortic and pulmonary artery catheters were used to obtain blood samples to measure systemic arterial and mixed venous blood gases, respectively. Systemic arterial and mixed venous pH, carbon dioxide tension (P CO₂), and oxygen tension (P O₂) were measured using an ABL-600 (Radiometer, Copenhagen, Denmark). Oxygen-hemoglobin saturation (S O₂) was measured using a Hemoximeter OSM-3 (Radiometer).

Experimental Protocols

All experiments were performed with each healthy, long-term instrumented dog lying on its right side in a quiet laboratory environment. Conscious dogs were not sedated. Muscle relaxants were not used in these studies. Left pulmonary vascular pressure-flow (LPQ) plots were used to assess the effects of the various interventions on the pulmonary circulation. LPQ plots were constructed by continuously measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure [PAP] – left atrial pressure [LAP]) and LQ during gradual (approximately 1 min) inflation of the hydraulic occluder implanted around the right main pulmonary artery. This technique for measuring the LPQ relation is highly reproducible and has little or no effect on systemic hemodynamics, blood gases, or the zonal condition of the lung.6

Protocol 1: Effects of Propofol Anesthesia on the Pulmonary Vasodilator Response to Acetylcholine.

We investigated the effects of propofol anesthesia on the pulmonary vascular response to cumulative doses of the endothelium-dependent vasodilator acetylcholine after preconditioning with the thromboxane analog 9,11-dideoxy-11 a,9 a-epoxymethano-prostaglandin F 2α (U46619; a gift from Cayman Chemical, Ann Arbor, MI). A baseline LPQ plot was first obtained in each conscious dog (n = 8). U46619 was then administered (0.17 ± 0.02 μg · kg⁻¹ · min⁻¹ intravenously) to preconstrict the pulmonary circulation before acetylcholine administration. 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 acetyl-
PROPOFOL ATTENUATES PULMONARY VASODILATION

choline (0.01, 0.1, 1.0, and 10 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) intravenously) during its cumulative administration (approximately 15 min at each dose) while the infusion of U46619 was continued. We previously verified that pulmonary vasoconstriction induced by U46619 is stable during the time course of this protocol.7

On a different day, this protocol was repeated in the same eight dogs during propofol anesthesia. Anesthesia was induced by bolus injection of propofol (5.0 mg/kg intravenously). An endotracheal tube was placed, and ventilation was controlled with a respirator with zero end-expiratory pressure. Immediately after intubation, we started and continued the intravenous infusion of propofol (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 to 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 at least 30 min to achieve steady state conditions. During propofol anesthesia, the dose of U46619 (0.09 \( \pm 0.02 \mu g \cdot kg^{-1} \cdot min^{-1} \) intravenously) 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 acetylcholine at the same level of vasomotor tone in the conscious and propofol-anesthetized states.

We investigated the effects of intralipid vehicle (Cleveland Clinic Pharmacy, Cleveland, OH) on the pulmonary vascular response to cumulative doses of acetylcholine during preconstriction with U46619. It has been reported that intralipid can exert a vasoconstrictor response after preconstriction with U46619.8 In each conscious dog (n = 4), LPQ plots were obtained during the baseline condition, during preconstriction with U46619 (0.13 \( \pm 0.02 \mu g \cdot kg^{-1} \cdot min^{-1} \) intravenously), and during the cumulative (approximately 15 min at each dose) administration of acetylcholine (0.01, 0.1, 1.0, and 10 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) intravenously). On a different day, this protocol was repeated in the same four dogs in the conscious state during the intravenous administration of intralipid (5.0 mg/kg bolus plus 0.5 mg \cdot kg^{-1} \cdot min^{-1} infusion). During intralipid administration, the dose of U46619 (0.10 \( \pm 0.02 \mu g \cdot kg^{-1} \cdot min^{-1} \) intravenously) was titrated to achieve the same degree of preconstriction induced in the conscious state without intralipid administration.

We investigated the effects of propofol anesthesia on the pulmonary vascular response to cumulative doses of the endothelium-independent vasodilator proline–NO (a specific NO donor with an ultrashort half-life)5 in the presence of preconstriction with U46619. In each conscious dog (n = 6), LPQ plots were obtained in the baseline condition, during preconstriction with U46619 (0.13 \( \pm 0.02 \mu g \cdot kg^{-1} \cdot min^{-1} \) intravenously), and during the cumulative (approximately 15 min at each dose) administration of proline–NO (3, 6, 12, and 24 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) intravenously). On a different day, this protocol was repeated in the same six dogs during propofol anesthesia. Anesthesia with propofol was induced as described in protocol 1. During propofol anesthesia, the dose of U46619 (0.06 \( \pm 0.01 \mu g \cdot kg^{-1} \cdot min^{-1} \) intravenously) was titrated to achieve the same degree of preconstriction induced in the conscious state.

We investigated the effects of propofol anesthesia on the pulmonary vascular response to cumulative doses of the endothelium-dependent vasodilator bradykinin in the presence of preconstriction with U46619. In each conscious dog (n = 8), LPQ plots were obtained in the baseline condition, during preconstriction with U46619 (0.21 \( \pm 0.02 \mu g \cdot kg^{-1} \cdot min^{-1} \) intravenously), and during the cumulative (approximately 15 min at each dose) administration of bradykinin (1, 2, 5, and 10 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) intravenously). On a different day, this protocol was repeated in the same eight dogs during propofol anesthesia. Anesthesia with propofol was induced as described in protocol 1. During propofol anesthesia, the dose of U46619 (0.11 \( \pm 0.02 \mu g \cdot kg^{-1} \cdot min^{-1} \) intravenously) was titrated to achieve the same degree of preconstriction induced in the conscious state.

Drug Preparation
All solutions were prepared on the day of the experiment. U46619 and acetylcholine (Sigma Chemical, St.
Louis, MO) were diluted in 0.9% saline. Bradykinin (RBI, Natick, MA) was dissolved in sterile water and then diluted in 0.9% saline. Proline–NO (Cayman Chemical) was diluted in 0.1M NaOH. Propofol (2,6-diisopropylphenol) was purchased from Zeneca Pharmaceuticals (Wilmington, DE).

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 less than or equal to 0 mmHg) as a function of LQ in each individual experiment. In all protocols, the LPQ relation was linear by inspection over the empirically measured range of LQ. 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·min⁻¹·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. Multivariate analysis of variance in the form of the Hotelling T² was used to assess the effects of propofol, U46619, acetylcholine, proline–NO, and bradykinin within each group. Two-way analysis of variance followed by Student t test for paired comparisons was used to assess the effects of propofol anesthesia on the magnitude of the agonist-induced pulmonary vasodilator responses. All values are presented as the mean ± SEM.

Results
Propofol had no effect on the baseline LPQ relation compared with the conscious state (fig. 1). The dose of U46619 was titrated to achieve the same degree of preconstriction in the conscious and propofol-anesthetized states (fig. 1). In all protocols, a lower (P < 0.05) dose of U46619 was necessitated for preconstriction during propofol anesthesia compared with the conscious state.

Protocol 1: Effect of Propofol on Acetylcholine-induced Pulmonary Vasodilation
We tested the hypothesis that propofol would attenuate the response to the endothelium-dependent vasodilator acetylcholine. LPQ plots at baseline, during U46619 preconstriction, and during administration of acetylcholine (10 μg · kg⁻¹ · min⁻¹) in an individual dog in the conscious and propofol-anesthetized states are shown in figure 2. Summarized data for eight dogs are shown in fig. 1. Composite left pulmonary vascular pressure–flow (LPQ) plots at baseline and after preconstriction with U46619 (*P < 0.01) in the conscious state and during propofol anesthesia. Compared with the conscious state, propofol had no effect on the baseline LPQ relation. The dose of U46619 was titrated to achieve the same degree of preconstriction in the conscious and propofol-anesthetized states.

$$\frac{(PAP - LAP)_{U46619} - (PAP - LAP)_{acetylcholine, \ \text{proline-NO, \ \text{bradykinin}}}}{(PAP - LAP)_{U46619} - (PAP - LAP)_{\text{baseline}}} \times 100$$

Therefore, 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 Student t test for paired comparisons was used to assess the pulmonary vascular effects of acetylcholine, proline–NO, and bradykinin within each group. Two-way analysis of variance followed by Student t test for paired comparisons was used to assess the effects of propofol anesthesia on the magnitude of the agonist-induced pulmonary vasodilator responses. All values are presented as the mean ± SEM.

Anesthesiology, V 93, No 2, Aug 2000
PROPOFOL ATTENUATES PULMONARY VASODILATION

Protocol 2: Effect of Intralipid Vehicle on the Pulmonary Vasodilator Response to Acetylcholine

We tested the hypothesis that the intralipid vehicle was responsible for the attenuated response to acetylcholine during propofol anesthesia. However, figure 4B shows that acetylcholine-induced pulmonary vasodilation was not altered in conscious dogs during intralipid administration.

Protocol 3: Effect of Propofol on Proline-Nitric Oxide-induced Pulmonary Vasodilation

We tested the hypothesis that propofol would attenuate the pulmonary vascular response to the endothelium-independent vasodilator proline-NO. This agonist is a NO donor that directly activates vascular smooth muscle guanylyl cyclase to increase cyclic guanosine monophosphate and induce vasodilation. The proline-NO dose-response relation is summarized in figure 5. Proline-NO caused dose-dependent pulmonary vasodilation in the conscious state.
The consciousness state, and the magnitude of proline–NO–induced vasodilation was unaltered during propofol anesthesia.

Protocol 4: Effect of Propofol on Bradykinin-induced Pulmonary Vasodilation

We tested the hypothesis that propofol anesthesia caused a generalized decrease in endothelium-dependent pulmonary vasodilation. The bradykinin dose–response relation is summarized in figure 6. Bradykinin caused dose-dependent pulmonary vasodilation in the conscious state, and the magnitude of bradykinin-induced vasodilation was unaltered during propofol anesthesia.

Fig. 6. Bradykinin dose–response relation after preconstriction with U46619 in the conscious state and during propofol anesthesia. The vasodilator response to bradykinin is expressed as the percent decrease in preconstriction with U46619. Bradykinin–NO–induced pulmonary vasodilation (P < 0.05) was preserved during propofol anesthesia compared with the conscious state.

Steady State Hemodynamics and Blood Gases

Steady state hemodynamics and blood gas values are summarized in tables 1 and 2, respectively. Compared with the conscious state, propofol anesthesia decreased mean SAP in each condition. U46619 increased SAP and PAP and decreased LQ in both the conscious and propofol-anesthetized states. After U46619 preconstriction, only acetylcholine decreased SAP in the conscious state, whereas all three vasodilators decreased SAP during

Fig. 5. Proline–nitric oxide (NO) dose–response relation after preconstriction with U46619 in the conscious state and during propofol anesthesia. The vasodilator response to proline–NO is expressed as the percent decrease in preconstriction with U46619. Proline–NO–induced pulmonary vasodilation (P < 0.05) was preserved during propofol anesthesia compared with the conscious state.

Anesthesiology, V 93, No 2, Aug 2000
Table 1. Steady State Hemodynamics: Conscious State versus Administration of Propofol

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>U46619</th>
<th>Acetylcholine</th>
<th>Proline–nitric oxide</th>
<th>Bradykinin</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP (mmHg)</td>
<td>Conscious 93 ± 2</td>
<td>108 ± 2*</td>
<td>93 ± 3†</td>
<td>98 ± 2</td>
<td>102 ± 1</td>
</tr>
<tr>
<td></td>
<td>Propofol 82 ± 3µ</td>
<td>94 ± 3†</td>
<td>73 ± 9†</td>
<td>77 ± 4†</td>
<td>89 ± 4†</td>
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<tr>
<td>PAP (mmHg)</td>
<td>Conscious 16 ± 1</td>
<td>26 ± 1*</td>
<td>25 ± 2</td>
<td>20 ± 2†</td>
<td>24 ± 2</td>
</tr>
<tr>
<td></td>
<td>Propofol 16 ± 1</td>
<td>27 ± 1*</td>
<td>31 ± 2†</td>
<td>21 ± 1†</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>LAP (mmHg)</td>
<td>Conscious 4 ± 1</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>2 ± 1</td>
<td>1 ± 1†</td>
</tr>
<tr>
<td></td>
<td>Propofol 3 ± 1</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>3 ± 1</td>
<td>3 ± 1†</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>Conscious 105 ± 3</td>
<td>94 ± 3*</td>
<td>112 ± 6†</td>
<td>108 ± 7</td>
<td>144 ± 8†</td>
</tr>
<tr>
<td></td>
<td>Propofol 110 ± 4</td>
<td>110 ± 4‡</td>
<td>127 ± 7</td>
<td>125 ± 3††</td>
<td>148 ± 9†</td>
</tr>
<tr>
<td>LQ (ml · min⁻¹ · kg⁻¹)</td>
<td>Conscious 74 ± 3</td>
<td>57 ± 3*</td>
<td>81 ± 7†</td>
<td>73 ± 4</td>
<td>87 ± 7†</td>
</tr>
<tr>
<td></td>
<td>Propofol 66 ± 3</td>
<td>59 ± 3*</td>
<td>77 ± 8†</td>
<td>69 ± 7</td>
<td>78 ± 5†</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.
Vasodilators = acetylcholine (10 µg · kg⁻¹ · min⁻¹), bradykinin (10 µg · kg⁻¹ · min⁻¹), proline–nitric oxide (24 nmol · kg⁻¹ · min⁻¹).
* P < 0.05 U46619 vs. baseline.
† P < 0.05 vasodilators vs. U46619.
‡ P < 0.05 propofol vs. conscious state.
HR = heart rate; LAP = mean left atrial pressure; LQ = mean left pulmonary blood flow; PAP = mean pulmonary arterial pressure; SAP = mean systemic arterial pressure.

Propofol anesthesia. Acetylcholine increased PAP during propofol, whereas proline–NO decreased PAP in both conditions. The vasodilators generally increased heart rate and LQ. Baseline blood gas values were similar in conscious and propofol-anesthetized dogs. U46619 caused a modest respiratory acidosis during propofol. After U46619 preconstriction, the vasodilators generally increased mixed venous PO₂ and SO₂ in both conditions.

Table 2. Steady State Blood Gases: Conscious State versus Administration of Propofol

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>U46619</th>
<th>Acetylcholine</th>
<th>Proline–nitric oxide</th>
<th>Bradykinin</th>
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<tr>
<td>Systemic arterial</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>pH</td>
<td>Conscious 7.40 ± 0.01</td>
<td>7.37 ± 0.01*</td>
<td>7.36 ± 0.01</td>
<td>7.39 ± 0.01†</td>
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</tr>
<tr>
<td></td>
<td>Propofol 7.41 ± 0.01</td>
<td>7.35 ± 0.01‡</td>
<td>7.34 ± 0.02</td>
<td>7.34 ± 0.02‡</td>
<td>7.34 ± 0.01‡</td>
</tr>
<tr>
<td>PCO₂ (mmHg)</td>
<td>Conscious 37 ± 1</td>
<td>38 ± 1</td>
<td>38 ± 2</td>
<td>35 ± 2</td>
<td>34 ± 1†</td>
</tr>
<tr>
<td></td>
<td>Propofol 36 ± 1</td>
<td>40 ± 1*‡</td>
<td>44 ± 2‡</td>
<td>45 ± 2‡</td>
<td>42 ± 1‡</td>
</tr>
<tr>
<td>PO₂ (mmHg)</td>
<td>Conscious 97 ± 1</td>
<td>83 ± 2*</td>
<td>80 ± 5</td>
<td>78 ± 4</td>
<td>83 ± 1</td>
</tr>
<tr>
<td></td>
<td>Propofol 99 ± 3</td>
<td>85 ± 3*</td>
<td>79 ± 7</td>
<td>80 ± 4</td>
<td>82 ± 2</td>
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<td>SO₂ (%)</td>
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<td>95 ± 1</td>
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<tr>
<td></td>
<td>Propofol 97 ± 1</td>
<td>94 ± 1*</td>
<td>90 ± 2†</td>
<td>92 ± 1</td>
<td>93 ± 1</td>
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<tr>
<td>Mixed venous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>Conscious 7.37 ± 0.01</td>
<td>7.33 ± 0.01*</td>
<td>7.33 ± 0.01</td>
<td>7.37 ± 0.01†</td>
<td>7.38 ± 0.02†</td>
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<tr>
<td></td>
<td>Propofol 7.38 ± 0.01</td>
<td>7.33 ± 0.01†</td>
<td>7.31 ± 0.02</td>
<td>7.32 ± 0.02‡</td>
<td>7.33 ± 0.01‡</td>
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<tr>
<td>PCO₂ (mmHg)</td>
<td>Conscious 44 ± 1</td>
<td>46 ± 1*</td>
<td>46 ± 2</td>
<td>41 ± 2†</td>
<td>39 ± 1†</td>
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<td></td>
<td>Propofol 42 ± 1</td>
<td>46 ± 1*</td>
<td>51 ± 2†</td>
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<td>41 ± 1*</td>
<td>47 ± 3</td>
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<td>SO₂ (%)</td>
<td>Conscious 68 ± 1</td>
<td>61 ± 1*</td>
<td>70 ± 1†</td>
<td>67 ± 5</td>
<td>74 ± 3†</td>
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<tr>
<td></td>
<td>Propofol 69 ± 1</td>
<td>61 ± 1*</td>
<td>63 ± 4</td>
<td>67 ± 2†</td>
<td>68 ± 2†</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.
* P < 0.05 U46619 vs. baseline.
† P < 0.05 vasodilators vs. U46619.
‡ P < 0.05 propofol vs. conscious state.
PO₂ = oxygen tension; PCO₂ = carbon dioxide tension; SO₂ = oxyhemoglobin saturation.

Discussion
Despite its widespread use in clinical anesthesia, there is a surprising paucity of information concerning the effects of propofol on endothelium-dependent vasodilation. Previous work in this area has exclusively involved the use of in vitro preparations. In rat thoracic aorta, propofol attenuated both endothelium-dependent (ace-
tylcholine) and -independent (sodium nitroprusside) vasorelaxation. Those investigators concluded that the effects of propofol were the result of suppression of NO function. Propofol also attenuated acetylcholine-induced relaxation in rabbit mesenteric artery. In contrast, propofol was found to increase basal NO production in cultured bovine aortic endothelial cells. Moreover, in rat distal coronary arteries, propofol-induced relaxation was found to be mediated by NO and prostacyclin. These conflicting studies make it difficult to generalize about the effects of propofol on endothelium-dependent vasodilation in the systemic vasculature.

The effects of propofol on the pulmonary circulation are also controversial. In humans, propofol has been reported to cause either a transient increase in pulmonary vascular resistance or pulmonary vasodilation in patients with an artificial heart. Pulmonary vasodilation has also been reported in perfused lung preparations and in isolated pulmonary arterial rings. In contrast, propofol had no effect on the baseline pulmonary vascular pressure-flow relation in pentobarbital-anesthetized dogs. We also reported that propofol had no effect on the baseline LPQ relation in long-term instrumented dogs, whereas it caused marked pulmonary vasoconstriction when vasomotor tone was increased. Only one previous study has investigated the effects of propofol on endothelium-dependent vasorelaxation in the pulmonary vasculature. In that study, which used precontracted rat pulmonary arterial rings, propofol caused an initial maximum vasorelaxation followed by an increase in tension toward the precontracted level. This effect was not observed in endothelium-denuded rings or in rings pretreated with an NO synthase inhibitor, which led these investigators to conclude that propofol inhibited the basal production of NO. Endothelium-dependent and -independent activators were not used in the study by Park et al. In conscious dogs, NO synthase inhibition has no effect on the baseline LPQ relation, which indicates that basal production of NO does not regulate the pulmonary circulation under resting conditions. This may explain why propofol had no effect on the baseline LPQ relation.

This is the first study to investigate the effects of propofol on endothelium-dependent vasodilation in an intact animal model. Long-term instrumentation allowed us to assess responses to endothelium-dependent and -independent vasodilators in the same animal in conscious and propofol-anesthetized states. Long-term instrumentation also obviated the need for background anesthetics, which are known to alter local mechanisms of pulmonary vasoregulation. The use of LPQ plots allowed us to distinguish between vasoactive and passive (flow-dependent) changes in pulmonary vascular resistance. Our results show that propofol causes a selective attenuation in the pulmonary vascular response to the endothelium-dependent vasodilator acetylcholine.

The normal pulmonary circulation has very little vaso- motor tone under resting conditions; therefore, it was necessary to preconstrict the pulmonary vasculature to assess the effects of propofol on the vasodilator agonists. We used the thromboxane mimic U46619 because it induces a rapid and sustained pulmonary vasoconstrictor response without increasing left atrial pressure. We were able to titrate the dose of U46619 to achieve the same degree of preconstriction in the conscious and propofol-anesthetized states. A lower dose of U46619 was necessitated to achieve preconstriction during propofol anesthesia. U46619-induced pulmonary vasoconstriction results in an increase in NO production, which acts to modulate the response to this stimulus. It seems likely that a lower dose of U46619 was necessitated to achieve preconstriction because endogenous NO-mediated vasodilation was attenuated during propofol anesthesia.

We used the NO donor proline–NO, to determine whether the attenuated response to acetylcholine during propofol anesthesia was caused by a defect in the pulmonary vascular smooth muscle cyclic guanosine monophosphate–mediated signaling pathway. We observed similar responses to this endothelium-independent vasodilator in conscious and propofol-anesthetized dogs, which indicates that propofol does not exert its effect on pulmonary vascular smooth muscle guanylyl cyclase activity. This result contrasts with a previous study in isolated thoracic aortic rings in which propofol was reported to attenuate the response to sodium nitroprusside. Interestingly, a component of sodium nitroprusside-induced pulmonary vasodilation is mediated by K⁺ATP channel activation. Moreover, we recently reported that propofol attenuates the pulmonary relaxant response to lemakalim, which is a K⁺ATP channel agonist. Taken together, these results may explain why propofol was observed to attenuate the response to sodium nitroprusside in thoracic aortic rings.

We also wanted to determine whether propofol caused a nonspecific decrease in endothelium-dependent pulmonary vasodilation; therefore, we assessed the response to bradykinin in conscious and propofol-anesthetized dogs. Acetylcholine and bradykinin stimulate endothelium-dependent pulmonary vasodilation by dif-
PROPFOLO ATTENUATES PULMONARY VASODILATION

Anesthesiology, V 93, No 2, Aug 2000

The vascular smooth muscle component of the response.

Bradykinin-induced endothelium-dependent pulmonary vasodilation is mediated by NO, prostacyclin, and a synergistic interaction between these two mediators that involves $K^{+}_{ATP}$ channel activation. In contrast, acetylcholine-induced pulmonary vasodilation is relatively insensitive to cyclooxygenase inhibition and $K^{+}_{ATP}$ channel inhibition and is mediated primarily by NO and an unidentified mediator that is sensitive to cytochrome P-450 inhibition. In contrast to acetylcholine, the pulmonary vasodilator response to bradykinin was similar in conscious and propofol-anesthetized dogs. These results indicate that propofol does not exert a nonspecific depressant effect on endothelium-dependent pulmonary vasodilation.

Intralipid had no effect on acetylcholine-induced pulmonary vasodilation in conscious dogs; therefore, the vehicle for propofol was not responsible for the attenuated response to acetylcholine. The normal responses to proline–NO and bradykinin indicate that propofol has a selective effect on the endothelial signaling pathway for acetylcholine-induced vasodilation. Acetylcholine stimulates membrane-bound muscarinic receptors on endothelial cells. Muscarinic receptor binding results in activation of guanine nucleotide regulatory protein, which couples activation of the receptor with subcellular effector systems. We reported preliminary results in isolated pulmonary arterial rings that suggest that propofol attenuates two components of acetylcholine-induced vasodilation that are sensitive to inhibition of NO synthase and cytochrome P-450. However, the upstream cellular mechanisms responsible for these effects have not been elucidated.

We can only speculate about the clinical significance of these findings. Endothelium-dependent vasodilation is an important endogenous mechanism that acts to counterbalance the response to vasoconstrictor stimuli. A decrease in endothelium-dependent pulmonary vasodilation would result in an enhanced response to a vasoconstrictor stimulus. This could have a deleterious effect in the setting of right ventricular dysfunction or heart failure. It is interesting to note that we previously observed a selective attenuation in endothelium-dependent pulmonary vasodilation in response to acetylcholine in conscious dogs after cardiopulmonary bypass.

Propofol causes a specific defect in the signal transduction pathway for acetylcholine-induced pulmonary vasodilation. This defect involves the endothelial and not the vascular smooth muscle component of the response.

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References

10. Nakayama M, Kondo U, Doi S, Murray PA: Pulmonary vasodilator response to adenosine triphosphate-sensitive potassium channel activation is attenuated during desflurane but preserved during sevoflurane anesthesia compared with the conscious state. Anesthesiology 1998; 88:1023–35


