

## ***Ketamine Preserves and Propofol Potentiates Hypoxic Pulmonary Vasoconstriction Compared with the Conscious State in Chronically Instrumented Dogs***

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**Background:** The authors tested the hypothesis that ketamine and propofol anesthesia would alter the magnitude of hypoxic pulmonary vasoconstriction compared with the conscious state. In addition, they assessed the extent to which cyclooxygenase pathway inhibition and adenosine triphosphate-sensitive potassium channel inhibition modulate hypoxic pulmonary vasoconstriction in the conscious state, and whether these pathways are altered during propofol anesthesia.

**Methods:** Twenty conditioned, male mongrel dogs were chronically instrumented to measure the left pulmonary vascular pressure-flow relationship. Pressure-flow plots were measured during normoxia and hypoxia (systemic arterial PO<sub>2</sub> reduced to about 60 and about 50 mmHg) on separate days in the conscious state, during ketamine anesthesia, and during propofol anesthesia. The effects of indomethacin and glibenclamide on the magnitude of hypoxic pulmonary vasoconstriction were also assessed in the conscious and propofol-anesthetized states.

**Results:** Neither ketamine nor propofol had an effect on the baseline pressure-flow relationship during normoxia compared with the conscious state. Hypoxia resulted in stimulus-dependent pulmonary vasoconstriction ( $P < 0.01$ ) in the conscious state. Compared with the conscious state, the magnitude of hypoxic pulmonary vasoconstriction was preserved during ketamine but was potentiated ( $P < 0.01$ ) during propofol anesthesia. Indomethacin enhanced ( $P < 0.01$ ) hypoxic pulmonary vasoconstriction in both the conscious and propofol-anesthetized states. In contrast, glibenclamide only enhanced ( $P <$

0.01) hypoxic pulmonary vasoconstriction in the conscious state and had no effect during propofol anesthesia.

**Conclusion:** Hypoxic pulmonary vasoconstriction is preserved during ketamine anesthesia but is potentiated during propofol anesthesia. The potentiated response during propofol anesthesia appears to be caused by inhibition of adenosine triphosphate-sensitive potassium channel-mediated pulmonary vasodilation. (Key words: Lung; pulmonary circulation; vasomotor tone.)

HYPOXIC pulmonary vasoconstriction (HPV) is an important homeostatic mechanism that optimizes the gas exchange function of the lung by diverting pulmonary blood flow away from poorly oxygenated regions to better ventilated regions. General anesthetics may impair arterial oxygenation *via* attenuation of HPV.<sup>1-3</sup> We recently reported that isoflurane anesthesia markedly attenuated the magnitude of HPV in chronically instrumented dogs.<sup>4</sup> In contrast, the magnitude of HPV was not altered during either sevoflurane or desflurane anesthesia.<sup>5</sup> Our present objective was to investigate the effects of intravenous anesthetics (ketamine and propofol) on the magnitude of HPV compared with the conscious state. Our results indicate that HPV is preserved during ketamine anesthesia, whereas the magnitude of HPV is potentiated during propofol anesthesia. Therefore, our second objective was to investigate the mechanism responsible for the propofol-induced potentiation of the HPV response. We tested the hypothesis that this effect of propofol resulted from inhibition of the modulating influence of endogenous pulmonary vasodilator mechanisms during HPV. Specifically, we assessed the extent to which cyclooxygenase pathway inhibition and adenosine triphosphate-sensitive potassium (K<sup>+</sup><sub>ATP</sub>) channel inhibition modulate HPV in the conscious state, and whether these pathways are altered during propofol anesthesia. We used an experimental preparation in which dogs were chronically instrumented to measure the left pulmonary vascular pressure-flow (LPQ) relationship. This chronic instrumentation allowed us to

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assess the HPV response in the same dog in the conscious and anesthetized states. This technique also avoids the use of background anesthetics and acute surgical trauma, which can modify neural,<sup>6</sup> humoral,<sup>7</sup> and local<sup>8</sup> mechanisms of pulmonary vascular regulation. Moreover, the use of LPQ plots allows us to distinguish between active and passive (flow-dependent) effects of physiologic and pharmacologic interventions on the pulmonary circulation. This is particularly important because the magnitude of HPV depends on the absolute level of pulmonary blood flow.<sup>4</sup>

## Materials and Methods

All surgical procedures and experimental protocols were approved by an institutional animal care and use committee.

### *Surgery for Chronic Instrumentation*

Twenty conditioned, male mongrel dogs ( $27 \pm 2$  kg) were premedicated with morphine sulfate (10 mg intramuscularly) and anesthetized with intravenous pentobarbital sodium (20 mg/kg) and fentanyl citrate (15  $\mu$ g/kg). After tracheal intubation, the lungs were mechanically ventilated. Anesthesia was maintained with halothane (about 1.2% end-tidal). 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 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 internal diameter; In Vivo Metric, Healdsburg, CA) was positioned loosely around the right main pulmonary artery, and an electromagnetic flow probe (10 mm internal diameter; 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 1 day after surgery. Morphine sulfate (10 mg) was administered intramuscularly after surgery for pain as required. Ampicillin (1 g), cefazolin (1 g), and gentamicin (80 mg) were administered intravenously during surgery and on a daily basis for 10 days after surgery. The dogs were allowed to recover for at least 2 weeks before experimentation.

### *Experimental Measurements*

Vascular pressures were measured by attaching the fluid-filled catheters to strain-gauge manometers (Isotec; Quest Medical, Allen, TX) and were referenced to atmospheric pressure with the transducers positioned at mid-chest at the level of the spine with the dogs in the right lateral position. Heart rate was calculated from the phasic systemic arterial pressure 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 *via* the thermal dilution technique. This was achieved by acutely inserting a 7-French balloon-tipped thermal dilution catheter into the pulmonary artery through a percutaneous jugular puncture after topical lidocaine anesthesia. The catheter was positioned 2–3 cm beyond the pulmonic valve. The implanted perivascular hydraulic occluder was then inflated to occlude the right main pulmonary artery completely, which directed total pulmonary blood flow through the left pulmonary artery (and flow probe). LQ was then measured by thermal dilution (HEMOPRO<sub>2</sub>; Spectramed, Oxnard, CA) with multiple 10-ml sterile injectates of 5% dextrose in water. Values for LQ were referenced to body weight ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ ). 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 ( $P_{\text{CO}_2}$ ), and oxygen tension ( $P_{\text{O}_2}$ ) were measured with an ABL-600 (Radiometer, Copenhagen, Denmark). Oxyhemoglobin saturation ( $S_{\text{O}_2}$ ) was measured with a Hemoximeter 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, and anesthetized dogs were not paralyzed. LPQ plots were used to assess the effects of the various physiologic and pharmacologic 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 to measure the LPQ relationship is highly reproducible and has little or no effect on systemic hemodynamics, blood gases, or the zonal condition of the lung.<sup>9</sup>

**Protocol 1: Stimulus–Response Relationship for Hypoxic Pulmonary Vasoconstriction in the Conscious State.** A baseline LPQ plot was obtained during normoxia in each conscious dog ( $n = 7$ ). A conical face mask was then placed over the dog's snout. Room air was administered *via* the mask using a semiclosed circulation system, and after 15 min a normoxia LPQ plot with face mask was obtained. The delivered room air was then blended with gases from sources consisting of 100% nitrogen, oxygen, or carbon dioxide. The gas flows were titrated to the fraction of inspired oxygen tension ( $F_{I_{O_2}} = 13.5 \pm 0.2$ ) that resulted in a gradual decrease in systemic arterial  $P_{O_2}$  to about 60 mmHg. After reaching a new steady state (about 15 min), a hypoxic LPQ plot was generated. The gas flows were then titrated to decrease systemic arterial  $P_{O_2}$  to  $\sim 50$  mmHg ( $F_{I_{O_2}} = 11.2 \pm 0.2$ ), and a second hypoxic LPQ plot was generated.

**Protocol 2: Effect of Ketamine Anesthesia on the Magnitude of Hypoxic Pulmonary Vasoconstriction.** To determine the conscious response to hypoxia, LPQ plots were generated in each dog ( $n = 6$ ) as described in protocol 1. On a different day, this protocol was repeated in the same six dogs during ketamine anesthesia. A baseline LPQ plot was generated during normoxia in the conscious state. Anesthesia was then induced and maintained with the intravenous administration of ketamine (5 mg/kg bolus and  $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  infusion). The trachea was intubated and ventilation was controlled with a respirator with zero end-expiratory pressure. Tidal volume was fixed at 15 ml/kg. Baseline systemic arterial blood gases were matched to values measured in the conscious state by adjusting the respiratory rate to between 10 and 20 breaths per minute and by supplying supplemental  $O_2$ . Inspiratory and end-tidal  $O_2$  and  $CO_2$  tension were monitored continuously at the adapter end of the endotracheal tube (Solar 7000; Marquette Electronics, Milwaukee, WI). Body temperature was monitored and maintained between 38 and 39°C with a warming blanket during the experiment. Twenty minutes after induction of ketamine anesthesia, an LPQ plot was generated. The hypoxic gas mixture was then administered as described in protocol 1, and LPQ plots were generated with systemic arterial  $P_{O_2}$  about 60 mmHg and about 50 mmHg.

**Protocol 3: Effect of Propofol Anesthesia on the Magnitude of Hypoxic Pulmonary Vasoconstriction.** To determine the conscious response to hypoxia, LPQ plots were obtained in each dog ( $n = 7$ ) as described in protocol 1. On a different day, a baseline LPQ plot was generated during normoxia in the conscious

state. After administration of propofol (5 mg/kg, intravenously), the trachea was intubated and ventilation was controlled as described in protocol 2. Intravenous propofol was infused continuously at the rate of  $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  immediately after intubation. Twenty minutes after induction, an LPQ plot was obtained during propofol anesthesia. The hypoxic gas mixture was then administered *via* the endotracheal tube. Once a steady state was obtained with systemic arterial  $P_{O_2} \sim 60$  mmHg and  $\sim 50$  mmHg, hypoxic LPQ plots were generated. The infusion rate for propofol was then increased to  $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , and after 15 min an LPQ plot was obtained with systemic arterial  $P_{O_2}$  about 50 mmHg. On a different day, we tested the effect of 10% intralipid vehicle (Cleveland Clinic Pharmacy, Cleveland, OH) on the HPV response in three of the dogs used in protocol 3. After obtaining a baseline LPQ plot, intralipid was administered intravenously at the dose corresponding to that used in the propofol protocol (5 mg/kg bolus and  $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  infusion). After 20 min, LPQ plots were obtained while the conscious dogs were breathing room air, room air *via* mask, and during hypoxia (systemic arterial  $P_{O_2}$  about 50 mmHg).

**Protocol 4: Effect of Propofol Anesthesia on the Magnitude of Hypoxic Pulmonary Vasoconstriction after Cyclooxygenase Pathway Inhibition.** Cyclooxygenase inhibition was achieved *via* the intravenous administration of indomethacin 5 mg/kg (Sigma Chemical Company, St. Louis, MO). This dose inhibits prostaglandin synthesis and abolishes the pulmonary pressor response to arachidonic acid.<sup>4</sup> Indomethacin was dissolved in sterile water with 114 g sodium carbonate. To determine the intact (no drug) response to hypoxia (systemic arterial  $P_{O_2}$  about 50 mmHg) in the conscious state, LPQ plots were generated in each dog ( $n = 7$ ) as described in protocol 1. On a different day, LPQ plots were generated in the same conscious dogs at baseline, 45 min after administration of indomethacin, while breathing room air *via* mask, and during hypoxia with systemic arterial  $P_{O_2}$  approximately 50 mmHg. This protocol was repeated on different days in the same 7 dogs during propofol anesthesia with or without pretreatment with indomethacin. Anesthesia with propofol (5 mg/kg plus  $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , intravenously) was induced and maintained as described in protocol 3. LPQ plots were generated at conscious baseline, 45 min after administration of indomethacin, 20 min after induction of propofol anesthesia, and during hypoxia with systemic arterial  $P_{O_2}$  at about 50 mmHg.

**Protocol 5: Effect of Propofol Anesthesia on the Magnitude of Hypoxic Pulmonary Vasoconstriction after  $K^+$ <sub>ATP</sub> Channel Inhibition.**  $K^+$ <sub>ATP</sub> channel inhibition was achieved *via* the intravenous administration of glibenclamide (3 mg/kg, Sigma). This dose inhibits the pulmonary vasodilator response to a selective activator of  $K^+$ <sub>ATP</sub> channels, lemakalim, in dogs.<sup>8</sup> Glibenclamide reduced blood glucose by 20 mg/dl 30 to 45 min after administration, but the dogs recovered promptly from the experiments and showed no adverse effects from  $K^+$ <sub>ATP</sub> channel inhibition. Glibenclamide was dissolved in 0.1 N NaOH and diluted in 5% dextrose. To determine the intact (no drug) response to hypoxia (systemic arterial  $P_{O_2}$  approximately 50 mmHg) in the conscious state, LPQ plots were generated in each dog ( $n = 6$ ) as described in protocol 1. On a different day, LPQ plots were generated in the same conscious dogs at baseline, while breathing room air *via* mask, 15 min after administration of glibenclamide, and during hypoxia with systemic arterial  $P_{O_2}$  about 50 mmHg. This protocol was repeated on different days in the same six dogs during propofol anesthesia with or without pretreatment with glibenclamide. Anesthesia with propofol (5 mg/kg plus 0.5 mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>, intravenously) was induced and maintained as described in protocol 3. LPQ plots were generated at conscious baseline, 20 min after induction of propofol anesthesia, 15 min after administration of glibenclamide, and during hypoxia with systemic arterial  $P_{O_2}$  approximately 50 mmHg.

#### Data Analysis

Phasic and mean vascular pressures and LQ were displayed continuously on an eight-channel strip-chart recorder (model 2800; Gould, Eastlake, OH). Mean values for LQ and vascular pressures were obtained using passive electronic filters with a 2-s time constant and were measured at end-expiration. 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 using software by Labview (Austin, TX). The LPQ relationship was measured continuously over the empirically measured range of LQ in each individual experiment. In all protocols, the LPQ relationship 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

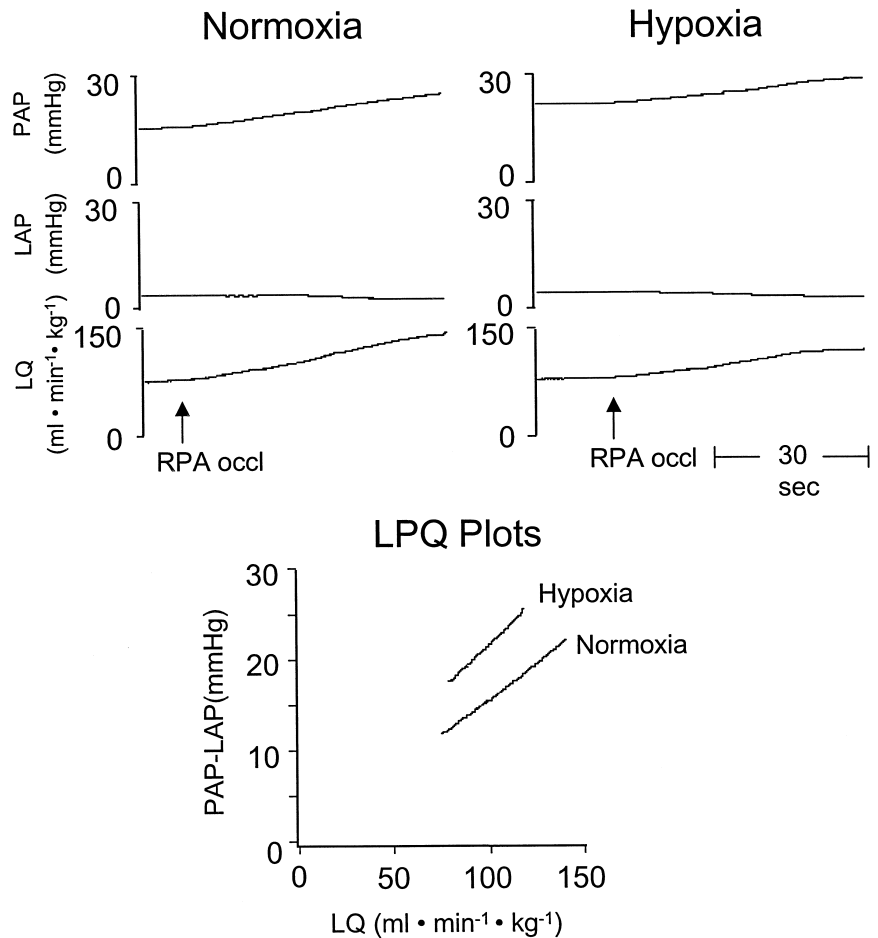
function of LQ in each individual experiment. The correlation coefficient for the LPQ relationship in each protocol averaged  $\geq$  0.98. The composite LPQ plots summarized in the figures were generated by using the regression parameters from each individual continuously measured LPQ plot to calculate PAP - LAP at 10 ml  $\cdot$  min<sup>-1</sup>  $\cdot$  kg<sup>-1</sup> 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 (ANOVA) in the form of Hotelling's  $T^2$  was used to assess the effects of the various interventions on the LPQ relationship. One-way ANOVA followed by Student *t* test for paired comparisons was used to assess the pulmonary vascular effects of hypoxia within each group. Two-way ANOVA followed by Student *t* test for paired comparisons was used to assess the effects of the anesthetics on the magnitude of HPV. All values are presented as means  $\pm$  SEM.

## Results

### *Protocol 1: The Magnitude of Hypoxic Pulmonary Vasoconstriction Depends on the Degree of Hypoxia in the Conscious State*

Figure 1 depicts mean values of PAP, LAP, and LQ, and the associated LPQ plots, in an individual conscious dog during normoxia and hypoxia. The LPQ plots were generated by gradual occlusion of the right pulmonary artery, which directs pulmonary blood flow through the left pulmonary artery and flow probe. In conscious dogs, breathing room air *via* face mask had no effect on the baseline normoxic LPQ relationship (fig. 2A). During hypoxia ( $P_{O_2}$  approximately 60 mmHg) there was a leftward shift ( $P < 0.01$ ) in the LPQ relationship, indicating HPV (fig. 2A). Decreasing  $P_{O_2}$  to 50 mmHg caused a further leftward shift ( $P < 0.01$ ) in the LPQ relationship (fig. 2A). The magnitude of the HPV response (*i.e.*, the increase in PAP - LAP from normoxia to hypoxia at each common value of LQ) was stimulus-dependent ( $P < 0.01$ ) and increased ( $P < 0.01$ ) as LQ increased at both levels of  $P_{O_2}$  (fig. 2B). Steady-state hemodynamics and blood gases are summarized in tables 1 and 2, respectively. Hypoxia increased PAP and heart rate, and decreased systemic arterial and mixed venous  $P_{O_2}$  and  $S_{O_2}$ . Hypoxia also caused a mild respiratory alkalosis in the conscious state.

**Fig. 1.** Mean values of pulmonary arterial pressure (PAP), left atrial pressure (LAP), and left pulmonary blood flow (LQ) before and during gradual right pulmonary artery occlusion (RPA occl) in an individual conscious dog during normoxia and hypoxia. The continuous left pulmonary vascular pressure–flow (LPQ) plots generated from these raw traces during normoxia and hypoxia are shown in the lower panel. Note that the LPQ plots are linear and that hypoxia caused a leftward shift in the LPQ relationship.



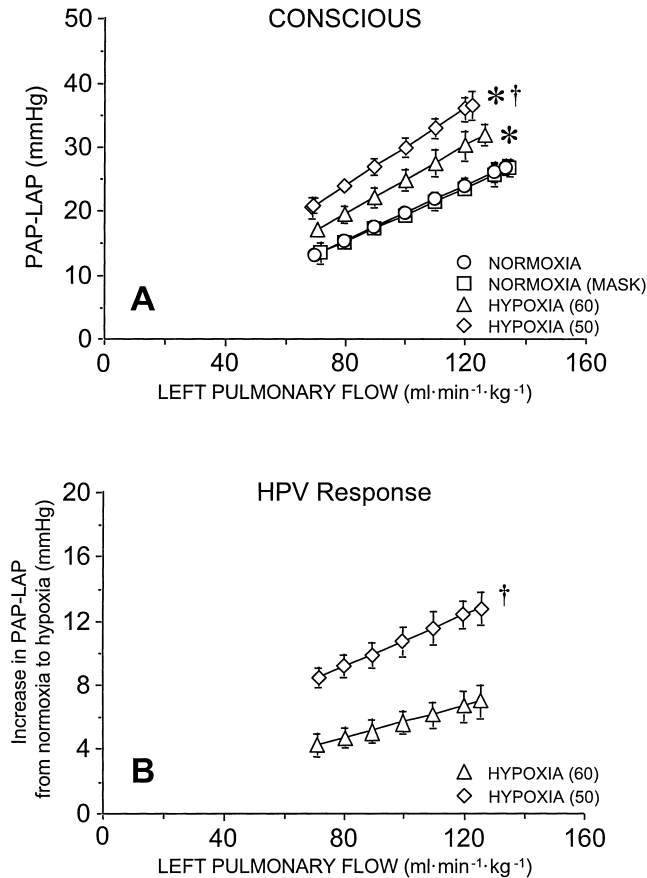
#### Protocol 2: Effect of Ketamine Anesthesia on the Magnitude of Hypoxic Pulmonary Vasoconstriction

Ketamine anesthesia had no effect on the baseline LPQ relationship during normoxia compared with the conscious state (fig. 3A). During ketamine anesthesia, hypoxia caused pulmonary vasoconstriction ( $P < 0.01$ ), which increased ( $P < 0.01$ ) as  $P_{O_2}$  decreased (fig. 3A). The HPV response during ketamine anesthesia was not significantly different from that measured in the conscious state (fig. 3B). Ketamine increased heart rate during both normoxia and hypoxia (table 1). Hypoxia increased PAP, but did not further increase heart rate, during ketamine anesthesia. Systemic arterial and mixed venous blood gases were similar during normoxia and hypoxia in the conscious and ketamine-anesthetized states (table 2).

#### Protocol 3: Effect of Propofol Anesthesia on the Magnitude of Hypoxic Pulmonary Vasoconstriction

Propofol anesthesia had no effect on the baseline LPQ relationship during normoxia compared to the conscious state (fig. 4A). During propofol anesthesia, hypoxia caused pulmonary vasoconstriction ( $P < 0.01$ ), which increased ( $P < 0.01$ ) as  $P_{O_2}$  decreased (fig. 4A). Increasing the dose of propofol did not further increase the HPV response (fig. 4A). The magnitude of the HPV response was potentiated ( $P < 0.01$ ) during propofol anesthesia compared to the conscious state (fig. 4B). Intralipid alone had no effect on the LPQ relationship during normoxia or hypoxia. Propofol decreased SAP and LQ during normoxia. Hypoxia increased PAP and heart rate to the same extent in conscious and propofol-anesthetized dogs. Systemic arterial and mixed venous blood gases were

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**Fig. 2. (A)** Composite left pulmonary vascular pressure-flow (LPQ) plots in seven dogs in the conscious state during normoxia, normoxia while breathing through a face mask, and hypoxia with systemic arterial  $P_{O_2}$  of 60 mmHg and 50 mmHg. Compared with normoxia, there was no change in the LPQ relationship during normoxia *via* mask. Hypoxia caused a leftward shift ( $*P < 0.01$ ) in the LPQ relationship, which indicates pulmonary vasoconstriction. There was a further shift ( $\dagger P < 0.01$ ) in the LPQ relationship as systemic arterial  $P_{O_2}$  decreased from 60 mmHg to 50 mmHg. **(B)** Composite hypoxic pulmonary vasoconstriction (HPV) response (increase in pulmonary arterial pressure - left atrial pressure from normoxia to hypoxia) as a function of left pulmonary flow. The magnitude of HPV was stimulus-dependent ( $\dagger P < 0.01$ ).

similar during normoxia and hypoxia in the conscious and propofol-anesthetized states.

*Protocol 4: Effect of Cyclooxygenase Inhibition on the Propofol-induced Potentiation of Hypoxic Pulmonary Vasoconstriction*

The effects of cyclooxygenase inhibition on the HPV response were assessed in the same chronically instrumented dogs studied in protocols 1 and 3. In the conscious state, cyclooxygenase inhibition with indomethacin

had no effect on the LPQ relationship during normoxia (fig. 5A), whereas the magnitude of HPV was enhanced ( $P < 0.01$ ) after cyclooxygenase inhibition (fig. 5B). Similar effects of indomethacin were observed during propofol anesthesia (fig. 6A and 6B). Indomethacin had no effect on baseline steady-state hemodynamics or blood gases. Changes in steady-state hemodynamics and blood gases in response to hypoxia were similar to those observed in protocols 1 and 3.

*Protocol 5: Effect of  $K^+_{ATP}$  Channel Inhibition on the Propofol-induced Potentiation of Hypoxic Pulmonary Vasoconstriction*

The effects of  $K^+_{ATP}$  channel inhibition on the HPV response were assessed in the same dogs studied in protocols 1 and 4. In the conscious state,  $K^+_{ATP}$  channel inhibition with glibenclamide had no effect on the LPQ relationship during normoxia (fig. 7A). The magnitude of HPV was enhanced ( $P < 0.01$ ) in the conscious state after  $K^+_{ATP}$  channel inhibition (fig. 7B). Glibenclamide had no effect on the LPQ relationship during normoxia in propofol-anesthetized dogs (fig. 8A). Moreover, glibenclamide had no effect on the HPV response during propofol anesthesia (fig. 8B). Glibenclamide had no effect on steady-state hemodynamics in the conscious state, but decreased ( $P < 0.05$ ) LQ in propofol-anesthetized dogs during both normoxia ( $65 \pm 2$  to  $43 \pm 2$  ml·min<sup>-1</sup>·kg<sup>-1</sup>) and hypoxia ( $63 \pm 8$  to  $47 \pm 2$  ml·min<sup>-1</sup>·kg<sup>-1</sup>). Changes in blood gases in response to hypoxia during protocol 5 were similar to those observed in protocols 1 and 3.

## Discussion

The main findings in this study are that (1) ketamine and propofol have no effect on the LPQ relationship during normoxia; (2) the magnitude of HPV is both stimulus- and flow-dependent in the conscious state and during ketamine and propofol anesthesia; (3) the magnitude of HPV is preserved during ketamine anesthesia and potentiated during propofol anesthesia; (4) vasodilator metabolites of the cyclooxygenase pathway and  $K^+_{ATP}$  channel activation modulate the HPV response in the conscious state; and (5) the modulating effect of  $K^+_{ATP}$  channel activation on the HPV response is not observed during propofol anesthesia.

We have previously reported that the magnitude of HPV increases as LQ increases in the conscious and isoflurane-anesthetized states,<sup>4</sup> as well as during sevoflu-

**Table 1. Steady-State Hemodynamics**

		Conscious	Ketamine	Conscious	Propofol
SAP (mmHg)	Normoxia	95 ± 2	101 ± 6	95 ± 3	82 ± 3†
	Hypoxia	100 ± 3	102 ± 9	99 ± 4	91 ± 7
PAP (mmHg)	Normoxia	15 ± 1	18 ± 1	15 ± 1	15 ± 1
	Hypoxia	24 ± 1*	27 ± 1*	24 ± 1*	25 ± 4*
LAP (mmHg)	Normoxia	3 ± 1	4 ± 1	3 ± 1	3 ± 1
	Hypoxia	3 ± 1	3 ± 1	3 ± 1	2 ± 1
HR (beats/min)	Normoxia	99 ± 4	164 ± 13†	97 ± 5	109 ± 10
	Hypoxia	119 ± 8*	182 ± 8†	120 ± 7*	135 ± 5*
LQ (ml · min <sup>-1</sup> · kg <sup>-1</sup> )	Normoxia	72 ± 5	76 ± 7	69 ± 5	56 ± 3†
	Hypoxia	73 ± 3	77 ± 9	67 ± 5	61 ± 4

Values are mean ± SEM. Hypoxia data for P<sub>O<sub>2</sub></sub> = 50 mmHg. Propofol data for dose of 5 mg/kg bolus and 0.5 mg · kg<sup>-1</sup> · min<sup>-1</sup> infusion.

SAP = mean systemic arterial pressure; PAP = mean pulmonary arterial pressure; LAP = mean left atrial pressure; HR = heart rate; LQ = mean left pulmonary blood flow.

\* *P* < 0.05 hypoxia versus normoxia.

† *P* < 0.05 anesthesia versus conscious.

rane and desflurane anesthesia.<sup>5</sup> The results of the present study extend these observations to the ketamine- and propofol-anesthetized states. The dependence of the HPV response on LQ underscores the importance of comparing the HPV response at the same level of flow when assessing the effects of anesthetics and other interventions on HPV. One advantage of utilizing LPQ plots is that they allow one to assess the effects of an intervention on the pulmonary vascular pressure gradient at a common value of LQ.

We observed a significant and reproducible HPV response when systemic arterial P<sub>O<sub>2</sub></sub> was decreased to

approximately 60 mmHg, and the magnitude of HPV was increased further when P<sub>O<sub>2</sub></sub> was decreased to approximately 50 mmHg. We have consistently observed a robust HPV response in conscious dogs,<sup>4,5</sup> whereas isolated canine lungs have been reported to exhibit a relatively weak HPV response.<sup>10</sup> The magnitude of the HPV response is determined by the alveolar P<sub>O<sub>2</sub></sub>,<sup>11</sup> and to a lesser extent by the P<sub>O<sub>2</sub></sub> of pulmonary arterial (mixed venous) blood.<sup>12</sup> There were no differences in systemic arterial or mixed venous P<sub>O<sub>2</sub></sub> during normoxia or hypoxia among the conscious, ketamine-anesthetized, or propofol-anesthetized states. Thus, the hypoxic stimulus was

**Table 2. Steady-State Blood Gases**

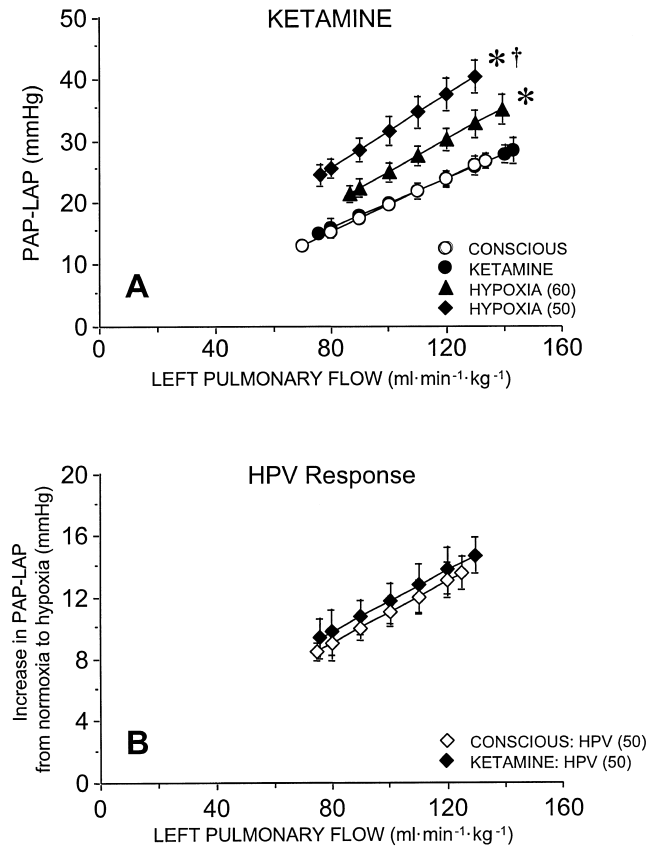
		Conscious	Ketamine	Conscious	Propofol
Systemic arterial pH	Normoxia	7.38 ± 0.01	7.39 ± 0.01	7.38 ± 0.01	7.38 ± 0.01
	Hypoxia	7.43 ± 0.01*	7.41 ± 0.01	7.43 ± 0.02*	7.39 ± 0.01
P <sub>CO<sub>2</sub></sub> (mmHg)	Normoxia	40 ± 1	38 ± 1	40 ± 1	38 ± 1
	Hypoxia	36 ± 1*	36 ± 1	37 ± 2*	37 ± 1
P <sub>O<sub>2</sub></sub> (mmHg)	Normoxia	96 ± 3	98 ± 3	96 ± 1	93 ± 2
	Hypoxia	49 ± 1*	50 ± 1*	50 ± 1*	48 ± 1*
S <sub>O<sub>2</sub></sub> (%)	Normoxia	97 ± 1	98 ± 1	97 ± 1	97 ± 1
	Hypoxia	79 ± 1*	78 ± 1*	79 ± 1*	77 ± 2*
Mixed venous pH	Normoxia	7.34 ± 0.01	7.36 ± 0.01	7.34 ± 0.01	7.36 ± 0.01
	Hypoxia	7.39 ± 0.01*	7.37 ± 0.01	7.39 ± 0.02*	7.37 ± 0.01
P <sub>CO<sub>2</sub></sub> (mmHg)	Normoxia	47 ± 1	42 ± 1	47 ± 1	42 ± 1
	Hypoxia	40 ± 1*	41 ± 1	41 ± 2*	41 ± 1
P <sub>O<sub>2</sub></sub> (mmHg)	Normoxia	46 ± 1	48 ± 2	46 ± 1	44 ± 2
	Hypoxia	32 ± 1*	35 ± 1*	32 ± 1*	32 ± 1*
S <sub>O<sub>2</sub></sub> (%)	Normoxia	69 ± 2	73 ± 3	69 ± 2	71 ± 1
	Hypoxia	48 ± 2*	52 ± 2*	48 ± 2*	50 ± 2*

Values are mean ± SEM.

P<sub>CO<sub>2</sub></sub> = carbon dioxide tension; P<sub>O<sub>2</sub></sub> = oxygen tension; S<sub>O<sub>2</sub></sub> = oxyhemoglobin saturation.

\* *P* < 0.05 hypoxia versus normoxia.

## HPV DURING KETAMINE AND PROPOFOL ANESTHESIA

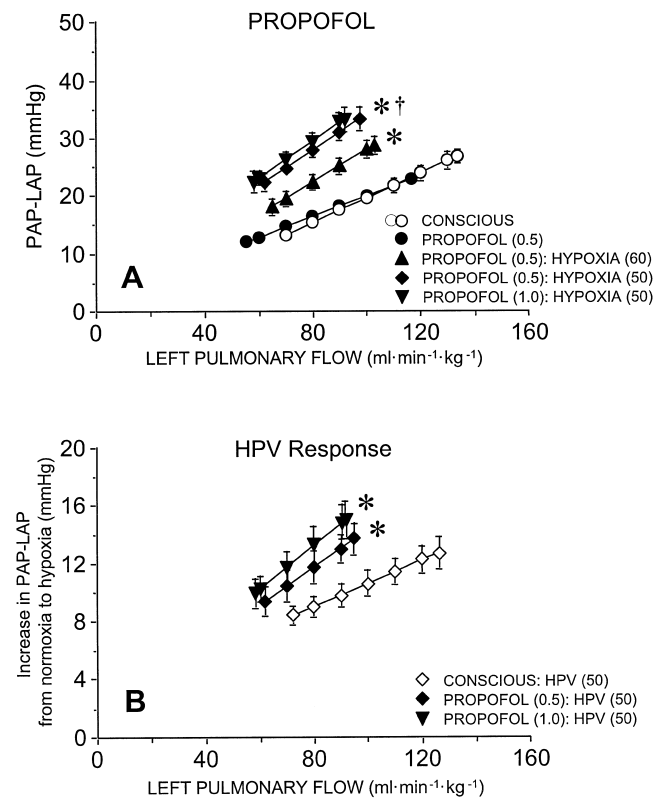


**Fig. 3. (A)** Composite left pulmonary vascular pressure–flow (LPQ) plots in six dogs during normoxia in the conscious state, during normoxia under ketamine anesthesia, and during hypoxia with systemic arterial  $P_{O_2}$  of 60 mmHg and 50 mmHg during ketamine anesthesia. Compared with normoxia in the conscious state, there was no change in the LPQ relationship during ketamine anesthesia. During ketamine anesthesia, hypoxia resulted in pulmonary vasoconstriction ( $*P < 0.01$ ), which increased ( $\dagger P < 0.01$ ) as systemic arterial  $P_{O_2}$  decreased from 60 mmHg to 50 mmHg. **(B)** Composite hypoxic pulmonary vasoconstriction (HPV) response at systemic arterial  $P_{O_2}$  of 50 mmHg as a function of left pulmonary flow in the conscious state and during ketamine anesthesia. During ketamine anesthesia, the HPV response was preserved compared with that measured in the conscious state.

the same in all three conditions. We did observe a mild respiratory alkalosis during hypoxia in the conscious state. Alkalosis can lead to an attenuation of the HPV response.<sup>13</sup> However, the degree of alkalosis was very mild, and systemic arterial  $P_{CO_2}$  during hypoxia was essentially identical among the three conditions.

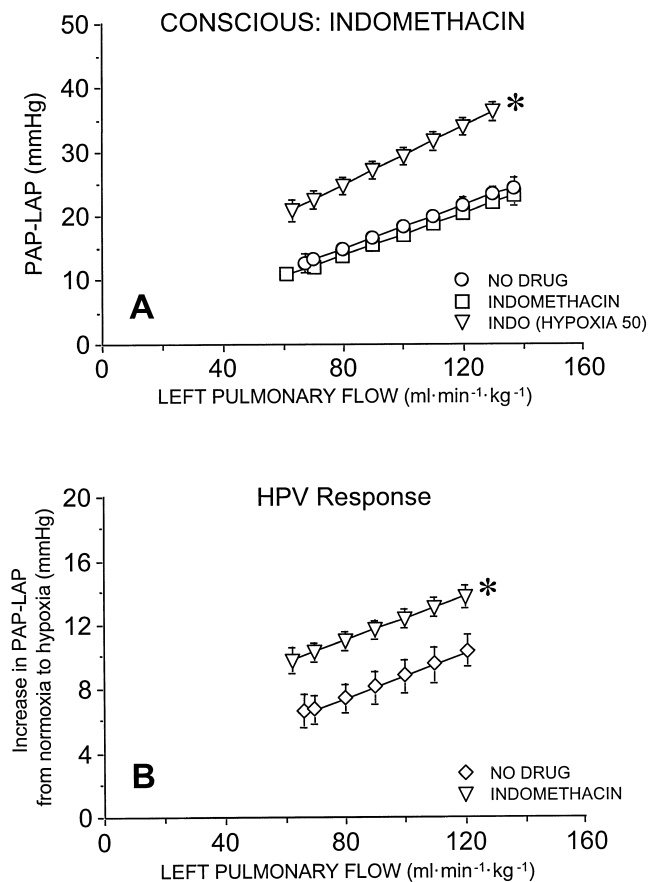
Ketamine had no effect on the baseline LPQ relationship during normoxia in the present study. This result was expected because the pulmonary circulation has little vasomotor tone under baseline conditions in this experimental model. Several clinical studies have suggested that ketamine may induce a small increase in

calculated pulmonary vascular resistance,<sup>14,15</sup> although it is unclear whether these changes reflect a direct effect of ketamine on pulmonary vasomotor tone. Ketamine caused dose-dependent relaxation in precontracted rat<sup>16</sup> and rabbit<sup>17</sup> pulmonary arterial rings. Ketamine also induced dose-dependent pulmonary vasodilation in isolated precontracted rat lungs.<sup>18,19</sup> Moreover, this effect was inhibited by verapamil,<sup>19</sup> which suggests that ketamine may compete with  $Ca^{2+}$  at  $Ca^{2+}$  binding sites associated with L-type  $Ca^{2+}$  channels. We have recently



**Fig. 4. (A)** Composite left pulmonary vascular pressure–flow (LPQ) plots in seven dogs during normoxia in the conscious state, during normoxia under propofol anesthesia, during hypoxia with systemic arterial  $P_{O_2}$  of 60 mmHg and 50 mmHg under propofol anesthesia ( $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ), and during hypoxia ( $P_{O_2}$  50 mmHg) under propofol anesthesia ( $1.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). Compared with normoxia in the conscious state, there was no change in the LPQ relationship during propofol anesthesia. During propofol anesthesia, hypoxia resulted in pulmonary vasoconstriction ( $*P < 0.01$ ), which increased ( $\dagger P < 0.01$ ) as systemic arterial  $P_{O_2}$  decreased from 60 mmHg to 50 mmHg. Increasing the dose of propofol did not cause a further shift in the LPQ relationship during hypoxia. **(B)** Composite hypoxic pulmonary vasoconstriction (HPV) response at systemic arterial  $P_{O_2}$  of 50 mmHg as a function of left pulmonary flow in the conscious state and during propofol anesthesia. During propofol anesthesia, the HPV response was potentiated ( $*P < 0.01$ ) compared with that measured in the conscious state.



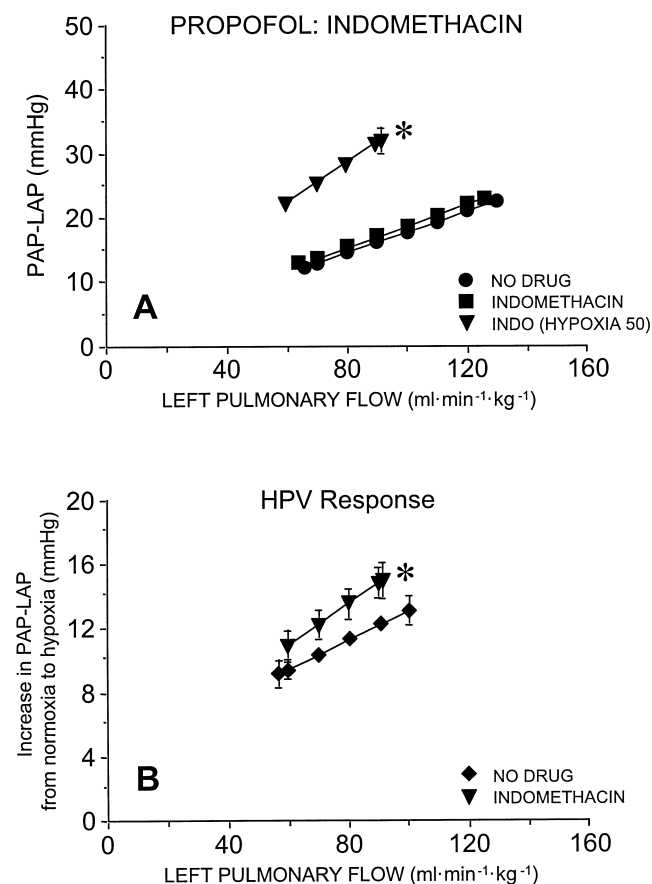


**Fig. 5. (A)** Composite left pulmonary vascular pressure–flow (LPQ) plots in seven conscious dogs during normoxia and hypoxia with or without pretreatment with indomethacin (INDO). Indomethacin had no effect on the LPQ relationship during normoxia compared to the no drug condition. Hypoxia caused a leftward shift ( $*P < 0.01$ ) in the LPQ relationship following indomethacin. **(B)** Composite hypoxic pulmonary vasoconstriction (HPV) response as a function of left pulmonary flow in the conscious state in the no drug condition and following indomethacin. The HPV response was potentiated ( $*P < 0.01$ ) following indomethacin compared with the no-drug condition.

reported that clinically relevant concentrations of ketamine inhibit the amplitude of phenylephrine-induced oscillations in intracellular free  $Ca^{2+}$  concentration in individual pulmonary artery smooth muscle cells.<sup>20</sup> However, neither nifedipine nor verapamil had an effect on the oscillations,<sup>21</sup> which suggests that voltage-operated  $Ca^{2+}$  channels did not mediate the inhibitory effect of ketamine on the oscillations. Ketamine had no effect on the magnitude of HPV in the present study. This result is consistent with previous experimental animal<sup>1,2</sup> and human<sup>22</sup> studies.

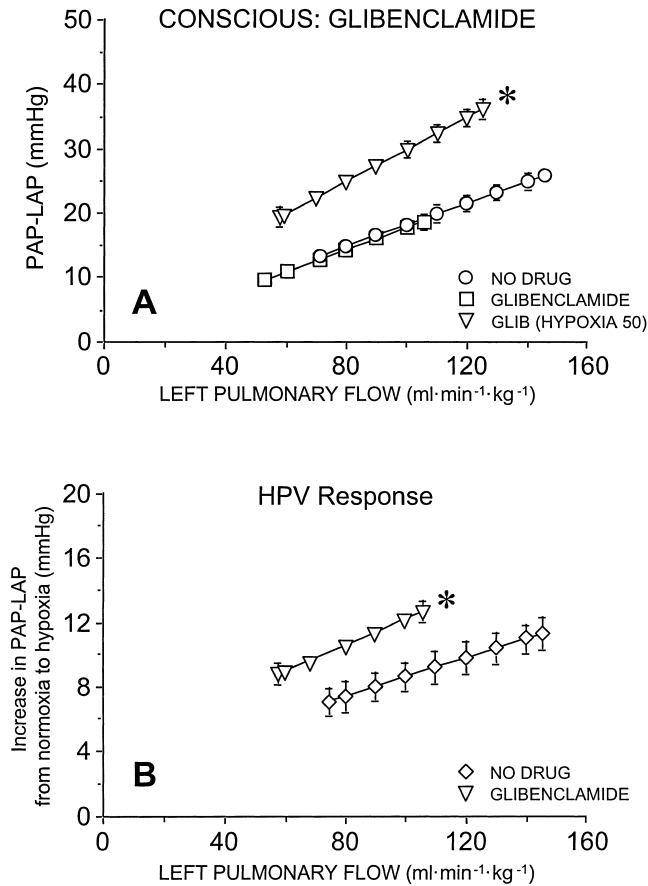
Propofol also had no effect on the baseline LPQ relationship during normoxia. Although propofol is gener-

ally recognized as a vasodilator in the systemic circulation,<sup>23,24</sup> there are conflicting reports concerning the pulmonary vascular effects of propofol. Propofol has been reported to cause a transient increase in pulmonary vascular resistance in humans,<sup>25</sup> whereas pulmonary vasodilation has been observed both in isolated perfused lungs<sup>18,26</sup> and in humans with artificial hearts.<sup>27</sup> Propofol has been shown to inhibit endothelium-dependent vasodilation,<sup>28</sup> which could theoretically result in pulmonary vasoconstriction. However, neither cyclooxygenase inhibition<sup>4</sup> nor nitric oxide synthase inhibition<sup>9</sup> have an effect on the baseline LPQ relationship in con-



**Fig. 6. (A)** Composite left pulmonary vascular pressure–flow (LPQ) plots in seven propofol-anesthetized dogs during normoxia and hypoxia with or without pretreatment with indomethacin (INDO). Indomethacin had no effect on the LPQ relationship during normoxia compared with the no-drug condition. Hypoxia caused a leftward shift ( $*P < 0.01$ ) in the LPQ relationship following indomethacin. **(B)** Composite hypoxic pulmonary vasoconstriction (HPV) response as a function of left pulmonary flow in the propofol-anesthetized state in the no-drug condition and following indomethacin. The HPV response was potentiated ( $*P < 0.01$ ) following indomethacin compared to the no-drug condition.

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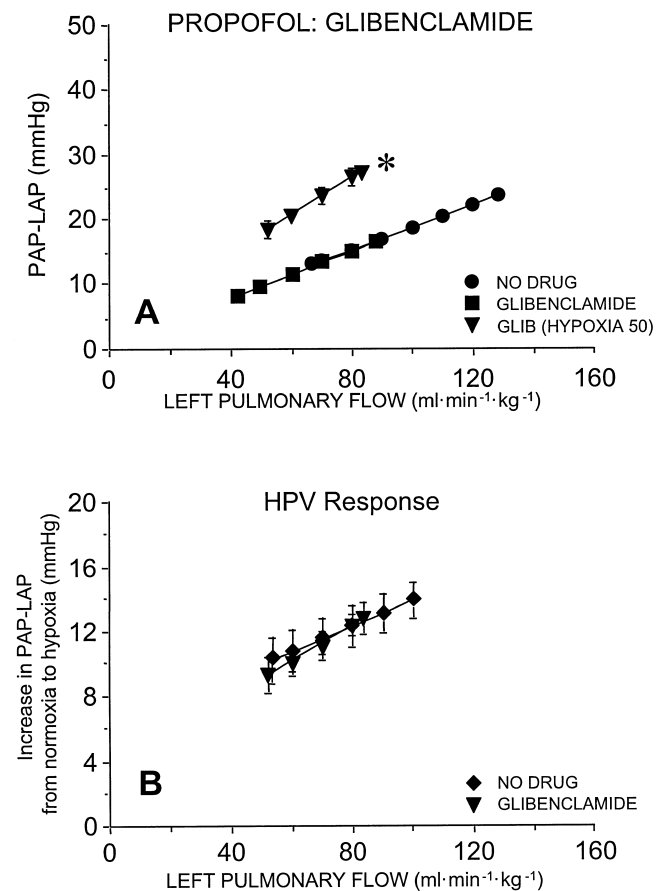
**Fig. 7. (A)** Composite left pulmonary vascular pressure–flow (LPQ) plots in six conscious dogs during normoxia and hypoxia with or without pretreatment with glibenclamide (GLIB). Glibenclamide had no effect on the LPQ relationship during normoxia compared with the no-drug condition. Hypoxia caused a leftward shift ( $*P < 0.01$ ) in the LPQ relationship following glibenclamide. **(B)** Composite hypoxic pulmonary vasoconstriction (HPV) response as a function of left pulmonary flow in the conscious state in the no-drug condition and following glibenclamide. The HPV response was potentiated ( $*P < 0.01$ ) following glibenclamide compared to the no-drug condition.

conscious dogs, so we predicted that propofol would not alter the baseline LPQ relationship.

In contrast to ketamine, the magnitude of HPV was increased during propofol anesthesia compared with the conscious state. This result conflicts with previous studies, in which propofol was observed to have no effect on the HPV response.<sup>29–31</sup> However, several factors may have influenced the results of those previous studies, including the presence of background anesthetics, acute surgical trauma, the lack of a conscious control group, and concomitant changes in cardiac output.

To investigate the mechanism responsible for the potentiated HPV response during propofol, we tested the

hypothesis that propofol attenuated the modulating influence of vasodilator metabolites of the cyclooxygenase pathway. Cyclooxygenase metabolites are released from hypoxic lungs,<sup>32</sup> and cyclooxygenase inhibition has been shown to potentiate the HPV response.<sup>33</sup> In the present study, we observed that cyclooxygenase pathway inhibition with indomethacin potentiated the HPV response in conscious dogs. Moreover, this effect was still apparent during propofol anesthesia, which indicates that inhibition of this mechanism does not play a primary role in the propofol-induced potentiation of HPV.



**Fig. 8. (A)** Composite left pulmonary vascular pressure–flow (LPQ) plots in six propofol-anesthetized dogs during normoxia and hypoxia with or without pretreatment with glibenclamide (GLIB). Glibenclamide had no effect on the LPQ relationship during normoxia compared with the no-drug condition. Hypoxia caused a leftward shift ( $*P < 0.01$ ) in the LPQ relationship following glibenclamide. **(B)** Composite hypoxic pulmonary vasoconstriction (HPV) response as a function of left pulmonary flow in the propofol-anesthetized state in the no-drug condition and following glibenclamide. The HPV response was not altered following glibenclamide compared with the no-drug condition.

We also tested the hypothesis that the potentiated HPV response during propofol was caused by an attenuation in  $K^+$ <sub>ATP</sub> channel mediated pulmonary vasodilation.  $K^+$ <sub>ATP</sub> channels have been identified in pulmonary vascular smooth muscle.<sup>34,35</sup> We recently reported that inhalational anesthetics can attenuate the pulmonary vasodilator response to an exogenously administered  $K^+$ <sub>ATP</sub> channel agonist.<sup>8</sup> Although  $K^+$ <sub>ATP</sub> channels have been reported to mediate anoxia-induced pulmonary vasodilation,<sup>36,37</sup> their role in the HPV response has not been investigated. In the present study,  $K^+$ <sub>ATP</sub> channel inhibition with glibenclamide had no effect on the baseline LPQ relationship in either the conscious or propofol-anesthetized states. Glibenclamide potentiated the HPV response in conscious dogs, which indicates that  $K^+$ <sub>ATP</sub> channel-mediated pulmonary vasodilation modulates the HPV response under these conditions. However, glibenclamide had no effect on the HPV response during propofol anesthesia. We recently demonstrated that propofol attenuates the vasorelaxant response to a  $K^+$ <sub>ATP</sub> channel agonist in isolated pulmonary arterial rings.<sup>38</sup> Taken together, these results suggest that propofol potentiates the magnitude of HPV by inhibiting endogenous  $K^+$ <sub>ATP</sub>-mediated pulmonary vasodilation.

Because propofol was in the same formulation used clinically, we assessed the effects of the vehicle for propofol. The solvent for propofol, intralipid emulsion, is known to cause an increase in PAP resulting from conversion of its precursor fatty acids (arachidonic acid and linoleic acid) to vasoactive metabolites.<sup>39</sup> However, in this study, intralipid emulsion had no effect on the LPQ relationship during normoxia or hypoxia in conscious dogs. The diluents for indomethacin and glibenclamide also had no effect on the LPQ relationship. Ketamine contains a preservative (not more than 0.1 mg/ml benzethonium chloride). Although we have not directly assessed the effects of this preservative on the LPQ relationship, ketamine (with preservative) had no effect on the LPQ relationship during normoxia or hypoxia.

The plasma concentration of propofol required to prevent the response to a surgical stimulus is approximately 6  $\mu$ g/ml in humans and dogs.<sup>40</sup> Because of the pharmacokinetic characteristics for propofol in dogs,<sup>40</sup> we chose an initial dose of 0.5 mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> in order to achieve an appropriate plasma concentration. Doubling the propofol infusion rate did not further potentiate the HPV response, so the initial dose may have been sufficient to induce the maximal effect. The dose of ketamine was chosen to provide reliable anesthesia in all dogs.

However, no direct conclusion about the relative anesthetic potencies of these intravenous anesthetics should be inferred. In contrast to propofol, ketamine caused a significant increase in heart rate, presumably because of the central and peripheral sympathomimetic actions of this drug.<sup>41</sup>

In summary, compared with the response measured in the conscious state, the magnitude of the HPV response was preserved during ketamine anesthesia and potentiated during propofol anesthesia. This latter effect does not primarily involve the cyclooxygenase pathway but appears to be mediated by a propofol-induced attenuation of  $K^+$ <sub>ATP</sub>-mediated pulmonary vasodilation.

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