

## Preservation of Hypoxic Pulmonary Vasoconstriction during Sevoflurane and Desflurane Anesthesia Compared to the Conscious State in Chronically Instrumented Dogs

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**Background:** The authors' objective was to assess the extent to which sevoflurane and desflurane anesthesia alter the magnitude of hypoxic pulmonary vasoconstriction compared with the response measured in the same animal in the conscious state.

**Methods:** Left pulmonary vascular pressure-flow plots were generated in seven chronically instrumented dogs by continuously measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure-left atrial pressure) and left pulmonary blood flow during gradual (~1 min) inflation of a hydraulic occluder implanted around the right main pulmonary artery. Pressure-flow plots were generated during normoxia and hypoxia on separate days in the conscious state, during sevoflurane (~3.5% end-tidal), and during desflurane (~10.5% end-tidal) anesthesia. Values are mean  $\pm$  SEM.

**Results:** In the conscious state, administration of the hypoxic gas mixture by conical face mask decreased ( $P < 0.01$ ) systemic arterial  $PO_2$  from  $94 \pm 2$  mmHg to  $50 \pm 1$  mmHg and caused a leftward shift ( $P < 0.01$ ) in the pressure-flow relationship, indicating pulmonary vasoconstriction. The magnitude of hypoxic pulmonary vasoconstriction in the conscious state was flow-dependent ( $P < 0.01$ ). Neither anesthetic had an effect on the baseline pressure-flow relationship during normoxia. The magnitude of hypoxic pulmonary vasoconstriction during sevoflurane and desflurane was also flow-dependent ( $P < 0.01$ ). Moreover, at any given value of flow the magnitude of hypoxic

pulmonary vasoconstriction was similar during sevoflurane and desflurane compared with the conscious state.

**Conclusion:** These results indicate that hypoxic pulmonary vasoconstriction is preserved during sevoflurane and desflurane anesthesia compared with the conscious state. Thus, inhibition of hypoxic pulmonary vasoconstriction is not a general characteristic of inhalational anesthetics. The flow-dependent nature of the response should be considered when assessing the effects of physiologic or pharmacologic interventions on the magnitude of hypoxic pulmonary vasoconstriction. (Key words: Homeostasis; pulmonary circulation; vasoregulation.)

HYPOXIC pulmonary vasoconstriction (HPV) is a homeostatic mechanism whereby a decrease in alveolar  $P_{O_2}$  leads to constriction of adjacent arterioles and a subsequent diversion of blood flow to better oxygenated regions of the lung.<sup>1</sup> General anesthesia or surgical manipulation may result in an attenuation of HPV, leading to impaired gas exchange and arterial hypoxemia. It is widely accepted that volatile anesthetics attenuate HPV,<sup>2-7</sup> although there are reports in the literature that are not consistent with this concept.<sup>8-10</sup> Sevoflurane and desflurane are volatile anesthetics being used with increasing frequency because of their cardiac stability, rapid induction, and speed of emergence. Sevoflurane and desflurane have been shown to inhibit HPV in isolated perfused lung preparations.<sup>11,12</sup> Our goal was to assess the effects of sevoflurane and desflurane anesthesia on the magnitude of HPV in intact dogs that had been chronically instrumented to measure the left pulmonary vascular pressure-flow (LPQ) relationship. This experimental model has several important advantages. The chronic instrumentation allowed us to avoid the effects of acute surgical trauma and to assess the HPV response in the same animal in the conscious state and during sevoflurane and desflurane anesthesia. It also obviated the need for background anesthetics, which are known to modify neural,<sup>13,14</sup> humoral,<sup>15,16</sup> and local<sup>17,18</sup> mechanisms of pulmonary vasoregulation. Moreover, the use

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of LPQ plots to assess the effects of these volatile anesthetics on HPV avoids the limitations inherent in the interpretation of single-point calculations of pulmonary vascular resistance.<sup>19</sup> This is particularly important because the magnitude of HPV depends on the absolute level of pulmonary blood flow.<sup>4</sup> Based on our recent finding that isoflurane anesthesia attenuates the magnitude of HPV,<sup>4</sup> we tested the hypothesis that this effect is a general characteristic of inhalational anesthetics. Surprisingly our results indicate that HPV is preserved during sevoflurane and desflurane anesthesia compared with the response measured in the conscious state.

## Materials and Methods

All surgical procedures and experimental protocols were approved by the Institutional Animal Care and Use Committee.

### *Surgery for Chronic Instrumentation*

Seven conditioned, male mongrel dogs (weight, 22–27 kg) were premedicated with morphine sulfate (10 mg, intramuscular) and anesthetized with intravenous pentobarbital sodium (20 mg/kg) and fentanyl citrate (15 µg/kg). After tracheal intubation, the lungs were mechanically ventilated. Anesthesia was maintained with halothane (~1.2% end-tidal). With the use of 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, left and right atrium, 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 loosely positioned 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 1 day after surgery. Morphine sulfate (10 mg, intramuscular) was administered after surgery for pain as required. Intravenous ampicillin (1 g), cefazolin (1 g), and gentamicin (80 mg) were administered 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<sup>TM</sup>, Quest Medical, Allen, TX). Vascular pressures were referenced to atmospheric pressure with the transducers positioned at midchest at the level of the spine with the dogs in the right lateral position. Heart rate (HR) 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 *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 anesthesia (lidocaine spray). 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 on healthy, chronically instrumented dogs lying on their 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 hypoxia, sevoflurane, and desflurane on the pulmonary circulation. LPQ plots were constructed by continuously measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure–left atrial pressure [PAP–LAP]) and LQ during gradual (~1 min) inflation of the hydraulic occluder implanted around the right main pulmonary artery. This technique is highly reproducible and has little or no



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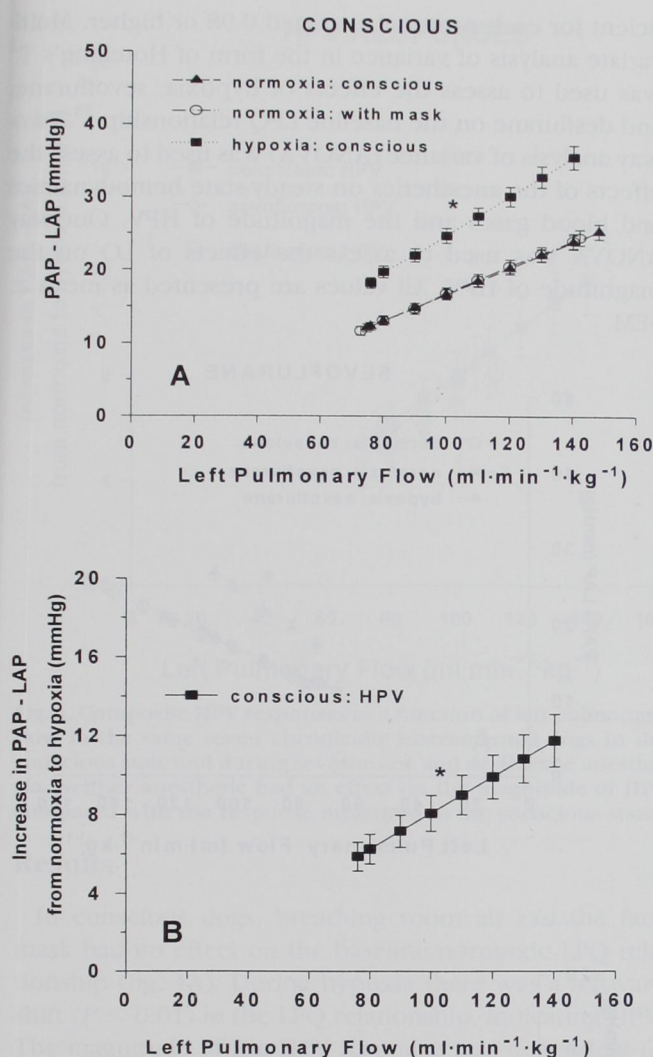


Fig. 1. (A) Composite left pulmonary vascular pressure-flow (LPQ) plots in seven dogs in the conscious state during normoxia, during normoxia with mask, and during hypoxia. Breathing room air through the face mask had no effect on the LPQ relationship. Compared with normoxia, hypoxia resulted in a leftward shift ( $P < 0.01$ ) in the LPQ relationship indicating pulmonary vasoconstriction. (B) Composite hypoxic pulmonary vasoconstriction (HPV) response (increase in PAP-LAP from normoxia to hypoxia) as a function of left pulmonary flow in seven conscious dogs. The magnitude of HPV was flow-dependent ( $P < 0.01$ ).

effect on systemic hemodynamics, blood gases, or the zonal condition of the lung.<sup>20</sup>

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 semi-closed circulation system, and after 10 min, a second normoxia LPQ plot with the face mask was obtained. The delivered room air

was then blended with gases from sources consisting of either 100% nitrogen, 100% oxygen, or 100% carbon dioxide. The gas flows were adjusted to achieve a gradual reduction in the fractional inspired O<sub>2</sub> tension (F<sub>I</sub>O<sub>2</sub>) and a consequent decrease in systemic arterial P<sub>O</sub><sub>2</sub> to ~50 mmHg. The F<sub>I</sub>O<sub>2</sub> during normoxia (22–25%) was decreased to 10–13% during hypoxia, as measured by mass spectrometry (Solar 7000, Marquette Electronics, Milwaukee, WI). After the attainment of a new steady-state (~10 min), a hypoxia LPQ plot was generated. Three LPQ plots were generated during hypoxia to verify the stability and reproducibility of the response.

On two separate days, this protocol was repeated in the same seven dogs during either sevoflurane or desflurane anesthesia. A baseline LPQ plot was first generated during normoxia in the conscious state. After a subanesthetic dose (4 mg/kg) of intravenous thiopental to minimize excitatory behavior, either sevoflurane or desflurane was administered *via* face mask. After attaining a deep anesthetic depth, the trachea was intubated (9 mm ID), and ventilation was controlled with zero end-expiratory pressure. Fresh gas flow was set at 100 ml·min<sup>-1</sup>·kg<sup>-1</sup>; tidal volume was set at 15 ml/kg, and either sevoflurane (Sevotec 3, Ohmeda, Austell, GA) or desflurane (Tec 6, Ohmeda) was delivered *via* a vaporizer. Body temperature was monitored and maintained between 38–39°C with a warming blanket during the course of the experiment. Systemic arterial blood gases were matched to values measured in the conscious state by supplying supplemental O<sub>2</sub> and by adjusting respiratory rate. Inspiratory and end-tidal P<sub>O</sub><sub>2</sub>, P<sub>CO</sub><sub>2</sub>, sevoflurane concentration, and desflurane concentration were monitored continuously at the adapter end of the endotracheal tube (Solar 7000). Both anesthetics were allowed to equilibrate for 1 h to achieve steady-state end-tidal concentrations of ~3.5% for sevoflurane and 10.5% for desflurane, which represents ~1.5 minimum alveolar

Table 1. Regression Parameters for Left Pulmonary Vascular Pressure-Flow Plots

		Slope (mmHg · ml <sup>-1</sup> · min <sup>-1</sup> · kg)	Intercept (mmHg)
Conscious	Normoxia	0.180 ± 0.009	-1.12 ± 0.65
	Normoxia-mask	0.181 ± 0.010	0.80 ± 0.50
	Hypoxia	0.274 ± 0.016*	-2.59 ± 0.73
Sevoflurane	Normoxia	0.167 ± 0.010	0.48 ± 0.81
	Hypoxia	0.267 ± 0.020*	-1.46 ± 1.91
Desflurane	Normoxia	0.184 ± 0.010	-0.65 ± 0.55
	Hypoxia	0.268 ± 0.020*	-2.08 ± 2.32

\*  $P < 0.01$ , hypoxia versus normoxia.



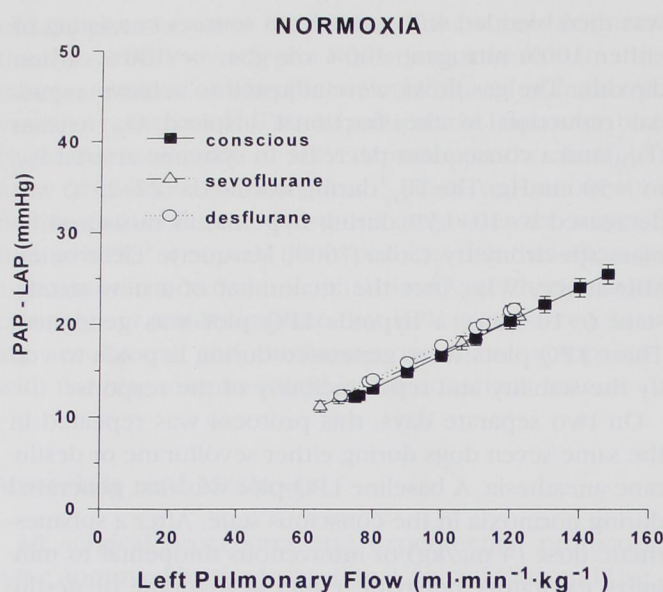


Fig. 2. Composite LPQ plots in the same seven dogs during normoxia in the conscious state, during sevoflurane anesthesia, and during desflurane anesthesia. Neither anesthetic had an effect on the LPQ relationship during normoxia.

concentration (MAC) for these anesthetics in dogs.<sup>21</sup> At this time, serum levels of thiopental are negligible.<sup>22</sup> A second LPQ plot was generated during normoxia in the sevoflurane- or desflurane-anesthetized states. The hypoxic gas mixture was then administered *via* the endotracheal tube as described above. Once a steady-state ( $\sim 10$  min) was achieved with systemic arterial  $P_{O_2} \sim 50$  mmHg, an LPQ plot was generated during the hypoxic anesthetized state. Once again, three LPQ plots were generated during hypoxia to verify the stability and reproducibility of the response.

#### Data Analysis

Phasic and mean vascular pressures and LQ were continuously displayed on an eight-channel strip-chart recorder (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. Vascular pressures were referenced to atmospheric pressure before and after each LPQ plot. The analog pressure and LQ signals were digitally converted and multiplexed (Medical Systems, PCM-8, Greenvale, NY) for later playback and analysis. 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  $LAP \leq 0$  mmHg) as a function of LQ in each individual experiment. The correlation coef-

ficient for each protocol averaged 0.98 or higher. Multivariate analysis of variance in the form of Hotelling's  $T^2$  was used to assess the effects of hypoxia, sevoflurane, and desflurane on the baseline LPQ relationship.<sup>23</sup> Two-way analysis of variance (ANOVA) was used to assess the effects of the anesthetics on steady-state hemodynamics and blood gases and the magnitude of HPV. One-way ANOVA was used to assess the effects of LQ on the magnitude of HPV. All values are presented as mean  $\pm$  SEM.

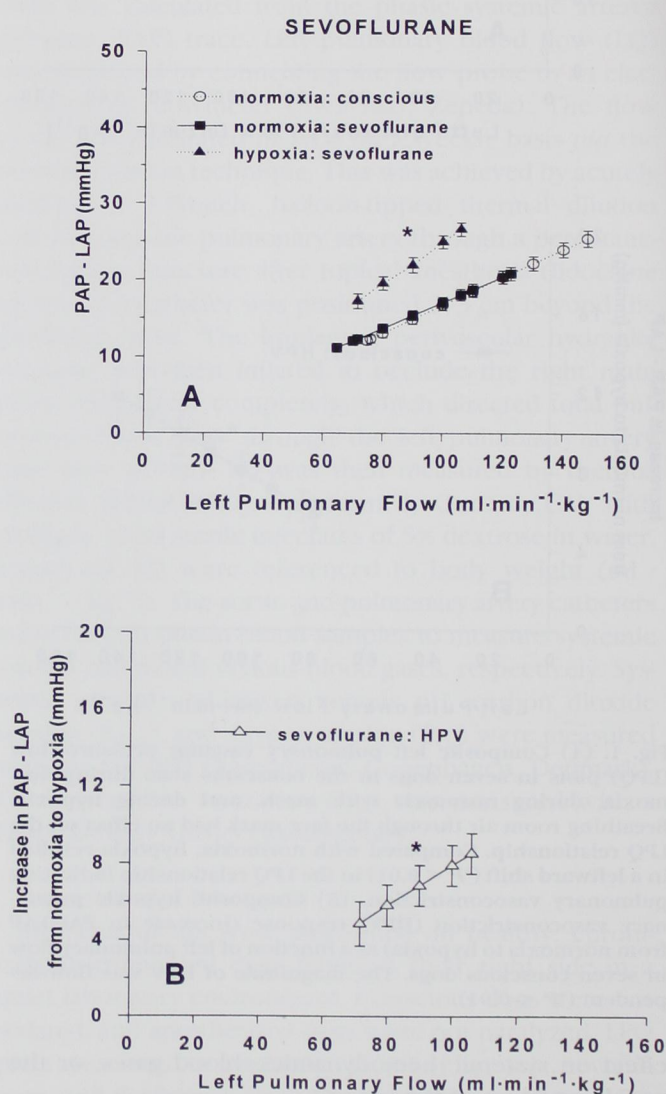


Fig. 3. (A) Composite LPQ plots in seven dogs in the conscious state during normoxia, normoxia with sevoflurane, and hypoxia with sevoflurane. During sevoflurane anesthesia, hypoxia resulted in a leftward shift ( $P < 0.01$ ) in the LPQ relationship indicating pulmonary vasoconstriction. (B) Composite HPV response as a function of left pulmonary flow in seven dogs during sevoflurane anesthesia. The magnitude of HPV was flow-dependent ( $P < 0.01$ ).



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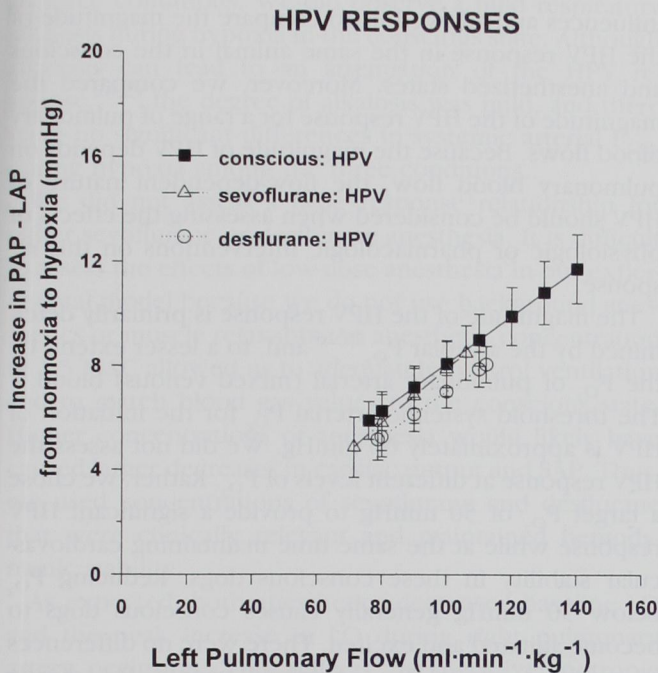


Fig. 4. Composite HPV responses as a function of left pulmonary flow in the same seven chronically instrumented dogs in the conscious state and during sevoflurane and desflurane anesthesia. Neither anesthetic had an effect on the magnitude of HPV compared with the response measured in the conscious state.

## Results

In conscious dogs, breathing room air *via* the face mask had no effect on the baseline normoxic LPQ relationship (fig. 1A). During hypoxia there was a leftward shift ( $P < 0.01$ ) in the LPQ relationship, indicating HPV. The magnitude of the HPV response was dependent ( $P < 0.01$ ) on the value of LQ (fig. 1B). The regression parameters for the LPQ relationship during normoxia and hypoxia are summarized in table 1.

The LPQ relationships during sevoflurane and desflurane anesthesia under normoxic conditions were not different from the baseline LPQ relationship during normoxia in the conscious state (fig. 2). During sevoflurane anesthesia, hypoxia caused a leftward shift ( $P < 0.01$ ) in the LPQ relationship, indicating pulmonary vasoconstriction (fig. 3A). The HPV response during sevoflurane anesthesia was also dependent ( $P < 0.01$ ) on LQ (fig. 3B). The magnitude of the HPV response during sevoflurane anesthesia was not significantly different from that measured in the conscious state (fig. 4).

During desflurane anesthesia, hypoxia again caused a leftward shift ( $P < 0.01$ ) in the LPQ relationship, indicating pulmonary vasoconstriction (fig. 5A). The HPV response during desflurane was dependent ( $P < 0.01$ )

on LQ (fig. 5B) and was not different from that measured in the conscious state (fig. 4).

Steady-state hemodynamics and blood gases are summarized in tables 2 and 3, respectively. Hypoxia in-

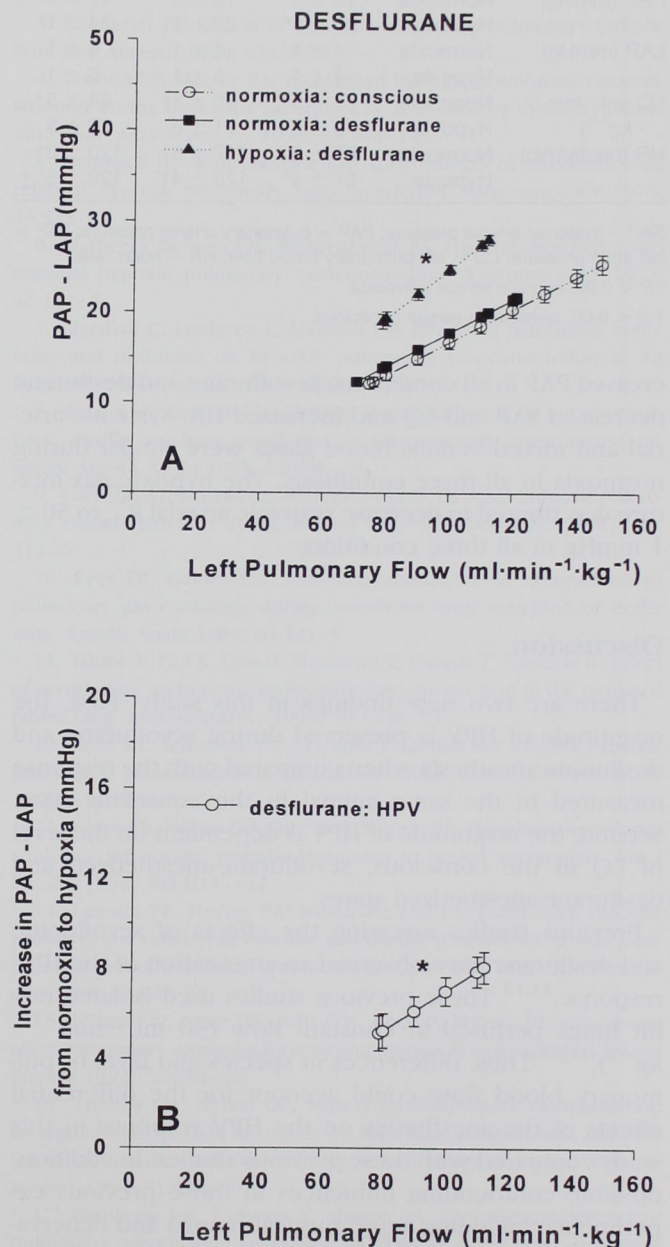


Fig. 5. (A) Composite LPQ plots in seven dogs in the conscious state during normoxia, normoxia with desflurane, and hypoxia with desflurane. During desflurane anesthesia, hypoxia resulted in a leftward shift ( $*P < 0.01$ ) in the LPQ relationship indicating pulmonary vasoconstriction. (B) Composite HPV response as a function of left pulmonary flow in seven dogs during desflurane anesthesia. The magnitude of HPV was flow-dependent ( $*P < 0.01$ ).



Table 2. Steady-state Hemodynamics

		Conscious	Sevoflurane	Desflurane
SAP (mmHg)	Normoxia	93 ± 6	74 ± 4†	77 ± 4†
	Hypoxia	100 ± 6	75 ± 4†	75 ± 4†
PAP (mmHg)	Normoxia	16 ± 1	15 ± 1	17 ± 1
	Hypoxia	23 ± 1*	23 ± 1*	24 ± 1*
LAP (mmHg)	Normoxia	4 ± 1	4 ± 1	6 ± 1
	Hypoxia	4 ± 1	5 ± 1	6 ± 1
LQ (ml · min <sup>-1</sup> · kg <sup>-1</sup> )	Normoxia	78 ± 3	65 ± 4†	64 ± 5†
	Hypoxia	79 ± 3	71 ± 5	76 ± 3
HR (beats/min)	Normoxia	87 ± 5	117 ± 5†	120 ± 3†
	Hypoxia	97 ± 4*	125 ± 4†	129 ± 5*,†

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

\*  $P < 0.05$ , hypoxia versus normoxia.

†  $P < 0.05$ , anesthesia versus conscious.

creased PAP in all conditions. Sevoflurane and desflurane decreased SAP and LQ and increased HR. Systemic arterial and mixed venous blood gases were similar during normoxia in all three conditions. The hypoxic gas mixture was titrated to decrease systemic arterial  $P_{O_2}$  to 50 ± 1 mmHg in all three conditions.

## Discussion

There are two new findings in this study. First, the magnitude of HPV is preserved during sevoflurane and desflurane anesthesia when compared with the response measured in the same animal in the conscious state. Second, the magnitude of HPV is dependent on the level of LQ in the conscious, sevoflurane-anesthetized and desflurane-anesthetized states.

Previous studies assessing the effects of sevoflurane and desflurane have observed an attenuation of the HPV response.<sup>11,12</sup> These previous studies used isolated rabbit lungs perfused at constant flow (30 ml · min<sup>-1</sup> · kg<sup>-1</sup>).<sup>11,12</sup> Thus, differences in species and level of pulmonary blood flow could account for the differential effects of the anesthetics on the HPV response in this study compared with these previous studies. In addition, possible confounding influences in those previous experiments, including acute surgical trauma and denervation, artificial nonpulsatile blood flow, presence of background anesthetics, application of PEEP, and lack of a conscious control, could explain the different findings. Acute experimental preparations may also result in the increased production of cyclooxygenase metabolites secondary to surgical manipulation and trauma.<sup>24</sup> Our experimental model avoids these potential confounding

influences and allowed us to compare the magnitude of the HPV response in the same animal in the conscious and anesthetized states. Moreover, we compared the magnitude of the HPV response for a range of pulmonary blood flows. Because the magnitude of HPV depends on pulmonary blood flow, the flow-dependent nature of HPV should be considered when assessing the effects of physiologic or pharmacologic interventions on this response.

The magnitude of the HPV response is primarily determined by the alveolar  $P_{O_2}$ <sup>25,26</sup> and, to a lesser extent, by the  $P_{O_2}$  of pulmonary arterial (mixed venous) blood.<sup>27</sup> The threshold systemic arterial  $P_{O_2}$  for the initiation of HPV is approximately 60 mmHg. We did not assess the HPV response at different levels of  $P_{O_2}$ . Rather, we chose a target  $P_{O_2}$  of 50 mmHg to provide a significant HPV response while at the same time maintaining cardiovascular stability in these conscious dogs. Reducing  $P_{O_2}$  below 50 mmHg generally causes conscious dogs to become agitated and excited. There were no differences in systemic arterial  $P_{O_2}$  or mixed venous  $P_{O_2}$  during normoxia or hypoxia among the three experimental conditions. Thus, the hypoxic stimulus was the same in

Table 3. Steady-state Blood Gases

		Conscious	Sevoflurane	Desflurane
Systemic arterial pH	Normoxia	7.40 ± 0.01	7.39 ± 0.01	7.39 ± 0.01
	Hypoxia	7.41 ± 0.01	7.40 ± 0.01	7.40 ± 0.01
$P_{CO_2}$ (mmHg)	Normoxia	41 ± 1	40 ± 2	38 ± 2
	Hypoxia	37 ± 1*	37 ± 1	35 ± 2
$P_{O_2}$ (mmHg)	Normoxia	94 ± 2	99 ± 2†	96 ± 3
	Hypoxia	50 ± 1*	50 ± 1*	50 ± 1*
$S_{O_2}$ (%)	Normoxia	97 ± 1	96 ± 1	96 ± 1
	Hypoxia	78 ± 1*	78 ± 1*	78 ± 1*
Mixed venous pH	Normoxia	7.37 ± 0.01	7.38 ± 0.02	7.36 ± 0.01
	Hypoxia	7.38 ± 0.01	7.36 ± 0.01	7.37 ± 0.01
$P_{CO_2}$ (mmHg)	Normoxia	45 ± 2	45 ± 2	42 ± 2
	Hypoxia	42 ± 1	44 ± 3	39 ± 2
$P_{O_2}$ (mmHg)	Normoxia	47 ± 2	48 ± 2	49 ± 3
	Hypoxia	35 ± 1*	34 ± 2*	36 ± 1*
$S_{O_2}$ (%)	Normoxia	73 ± 3	75 ± 3	74 ± 3
	Hypoxia	55 ± 2*	51 ± 2*	57 ± 2*

$P_{CO_2}$  and  $P_{O_2}$  = partial pressures of carbon dioxide and oxygen, respectively;  $S_{O_2}$  = oxyhemoglobin saturation.

\*  $P < 0.05$ , hypoxia versus normoxia.

†  $P < 0.05$ , anesthesia versus conscious.



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all three conditions. We did observe a mild respiratory alkalosis during hypoxia in the conscious state. Although alkalosis can lead to an attenuation of the HPV response,<sup>28,29</sup> the degree of alkalosis was mild, and there were no significant differences in systemic arterial  $P_{CO_2}$  during hypoxia among the three conditions.

We did not assess a dose-response relationship for either sevoflurane or desflurane anesthesia. It is difficult to assess the effects of low-dose anesthesia in our experimental model because we do not use background anesthetics or muscle relaxants. An anesthetic concentration of 1.5 MAC allowed us to adequately control ventilation and to match blood gas values to the conscious state. Higher concentrations of anesthesia would likely have caused larger decreases in cardiac output and SAP. Thus, we used concentrations of sevoflurane and desflurane that were clinically relevant and maintained hemodynamic stability.

As expected, both anesthetics decreased baseline LQ and the peak increase in LQ during right pulmonary artery occlusion. This reflects the negative inotropic effect of the anesthetics and the associated decrease in cardiac output. As a result, the HPV response was assessed for a smaller range of LQ during anesthesia. Because of the technique to generate LPQ plots, we were not able to assess the HPV response at values of LQ below baseline in the conscious or anesthetized states. The technique that we used to induce hypoxia resulted in systemic hypoxemia, so we do not know whether we can extrapolate these results to the setting of regional hypoxia without systemic hypoxemia. Finally, both anesthetics decreased SAP. The concomitant increase in HR likely reflects an increase in sympathetic nervous system activity. However, this appeared to have no effect on the baseline LPQ relationship during normoxia in anesthetized dogs compared with the conscious state.

In summary, neither sevoflurane nor desflurane anesthesia altered the baseline LPQ relationship during normoxia. The magnitude of the HPV response was dependent on the level of pulmonary blood flow in the conscious and anesthetized states. In addition, when compared to the conscious state, the magnitude of HPV was preserved during sevoflurane and desflurane anesthesia. Thus, attenuation of HPV is not a general characteristic of all inhalational anesthetics.

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